GENERAL LIBRARY
MAY 22 1919
UNIV. OF MICH.

VOLUME 23 NUMBER 5

ARCHIVES
OF
INTERNAL MEDICINE

EDITORIAL BOARD

JOSEPH L. MILLER, Chicago

RICHARD C. CABOT, Boston — LOUIS V. HAMMAN, Baltimore

GEORGE DOCK, St. Louis — WARFIELD T. LONGCOPE, New York

W. S. THAYER, Baltimore

MAY 15, 1919

PUBLISHED MONTHLY BY AMERICAN MEDICAL ASSOCIATION, 535 NORTH DEARBORN STREET, CHICAGO, ILLINOIS. ANNUAL SUBSCRIPTION, $5.00

Entered as Second Class Matter, January 23, 1909, at the Postoffice at Chicago, Illinois, Under Act of Congress of March 3, 1879. Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized on June 14, 1918.

CONTENTS OF PREVIOUS NUMBERS

DECEMBER, 1918. NUMBER 6

Intensive Study of Fifty Cases of Neurocirculatory Asthenia. Alfred Friedlander, M.D., and William Freyhof, M.D., Camp Sherman, Ohio.

The Comparative Food Value of Protein, Fat and Alcohol in Diabetes Mellitus as Measured by the Nitrogen Equilibrium. Herman O. Mosenthal, M.D., and George A. Harrop, Jr., M.D., Baltimore.

Contributions to the Physiology of the Stomach. Jacob Meyer, M.S., M.D., Chicago.

Tachycardia of Unknown Origin. Theodore B. Barringer, Jr., M.D., New York.

The Excretion of Creatin, Creatinin and Uric Acid in Acute Febrile Conditions. C. W. McClure, M.D., Bethlehem, Pa.

The Electrocardiogram in Thyroid Disease. Paul D. White, M.D., and Joseph C. Aub, M.D., Boston.

Renal Function as Measured by the Elimination of Fluids, Salt and Nitrogen, and the Specific Gravity of the Urine. Herman O. Mosenthal, M.D., Camp Gordon, Atlanta, Ga.

The Effect of Thymus Gland Injection on the Growth and Behavior of the Guinea-Pig. D. M. Olson, M.D., Chicago.

JANUARY, 1919. NUMBER 1

Observations on the Occurrence of Inverted and Diphasic P-Waves in Lead III of the Human Electrocardiogram. E. P. Carter, M.D., and A. M. Wedd, M.D., Pittsburgh.

Epidemic Cerebrospinal Meningitis as Observed at General Hospital No. 6, Fort McPherson, Ga., Winter of 1917 and 1918. C. N. B. Camac, M.D., and K. M. Bowman, M.D., Fort McPherson, Ga.

Further Studies Concerning the Essential Nature of Antitryptic Activity of Normal Serum and the Physiologic Function of Pancreatic Ferments. H. Wago, M.D., Chicago.

Chronic Capillary Cyanosis. L. Langstroth, M.D., San Francisco.

A Report on Goiter Among Draft Men from the Northwest. Frank P. Brendel and H. M. Helm, Fort McDowell, Calif.

Nonspecific Therapy in Arthritis and Infections. A Study of the Changes in the Blood Consequent on the Intravenous Injection of Typhoid Protein. A Consideration of the Analogy Between the Typhoid Paroxysm and the Malarial Paroxysm. D. M. Cowie, M.D., and H. Calhoun, M.D., Ann Arbor, Mich.

FEBRUARY, 1919. NUMBER 2

The Cause of the Reaction Following Transfusion of Citrated Blood. C. K. Drinker, M.D., and H. H. Brittingham, A.B., Boston.

The Chronic Form of Meningococcus Meningitis. Alfred Gordon, M.D., Philadelphia.

An Unusual Combination of Cardiac Arrhythmias of Atrial Origin Occurring in a Patient with Focal Infections and Thyroid Adenomata. L. F. Barker, M.D., and E. B. Richardson, M.D., Baltimore.

Pituitary Headaches and Their Cure. I. H. Pardee, M.D., New York.

Observations Concerning the Pathology of Pancreatic Ferments. H. Wago, M.D., Chicago.

The Physiologic Action of Cantharis. S. Mogulia, M.D., and A. L. Muirhead, M.D., Omaha.

Hydrocephalus and Choked Disk in Dogs. L. H. Kornder, M.D., Davenport, Iowa.

The Treatment of Bronchial Asthma with Vaccines. J. C. Walker, M.D., Boston.

Differentiation of Nephropathies, Cardiopathies and Allied Conditions by the Determination of Physical Constants. A. O. Gettler, Ph.D., and E. Oppenheimer, B. A., New York.

A Study on the Etiology of Cholecystitis and Its Production by the Injection of Streptococci. R. O. Brown, M.D., Rochester, Minn.

MARCH, 1919. NUMBER 3

The Standardization of Antipneumococcus and Antimeningitis Serums. A. B. Wadsworth, M.D., Mary B. Kirkbride and Ruth Gilbert, Albany, N. Y.

A Clinical Study of Meningitis Based on Two Hundred and Fifteen Cases. Major Willard J. Stone, M.D., and Major Ralph C. P. Truitt, M.D., Fort Riley, Kan.

Plasmaphaeresis in the Treatment of Chronic Nephritis and Uremia. James P. O'Hare, M.D., H. H. Brittingham, A.B., and C. K. Drinker, M.D., Boston.

Poliomyelitis, Clinically Atypical Because of Complicating Infection by a Proteus-Like Bacillus. Capt. O. T. Schultz, M.D., and Capt. A. M. Dannenberg, M.D., Camp Jackson, Columbia, S. C.

The Relative Frequency in Recruits With and Without Thyroid Enlargement of Certain Signs and Symptoms Which Occur in Neurocirculatory Asthenia. Capt. T. Addis and Capt. W. J. Kerr, Camp Lewis, American Lake, Wash.

Studies of the Chemistry of Pernicious Anemia. Max Kahn, M.D., Ph.D., and Joseph Baraky, M.D., New York.

Toxin Formation by a Variety of B. Botulinus When Cultivated Aerobically Under Various Conditions: Its Possible Production in the Animal Body. L. P. Shippen, M.D., Washington, D. C.

The Mechanism of the Protective Action of Carbohydrate Diet in Phosphorus and Chloroform Poisoning. J. P. Simonds, M.D., Chicago.

Experience with a Recent Epidemic of Meningococcic Meningitis Among a Chinese Civil Population. Peter K. Olitsky, M.D., New York.

Biochemical Studies of Pneumonic Exudates, with Special Reference to the Mechanism of the Crisis in Pneumonia. Studies in Pneumonia X. Charles Weiss, Ph.D., Philadelphia.

A Correction.

APRIL, 1919. NUMBER 4

Extrameningeal Meningococcus Infections. W. W. Herrick, M.D., New York.

Clinical Studies on the Effects of Louse Bites, Pediculus Corporis. Arthur D. Hirschfelder, M.D., and William Moore, A.B., Minneapolis.

Arborization Block. F. A. Willius, M.D., Rochester, Minn.

The Basal Metabolism in Anemia with Especial Reference to the Effect of Blood Transfusion on the Metabolism in Pernicious Anemia. Edna H. Tompkins, A.B., Harold H. Brittingham, A.B., and Cecil K. Drinker, M.D., Boston.

Studies on Alimentary Hyperglycemia and Glycosuria. C. V. Bailey, M.D., New York.

Diastatic Activity of the Blood in Cancer, Syphilis and Diabetes. H. H. DeNiord, M.D., and B. F. Schreiner, M.D., Buffalo.

Fatigue Disease as Exemplified in Functional Disorders of the Stomach and Thyroid Gland. John Rogers, M.D., New York.

The Plasma Chlorids in Anemia: an Experimental Study. Edward Steinfeld, M.D., Philadelphia.

The Clinical Significance of Slight Notching of the R-Wave of the Electrocardiogram. Alfred M. Wedd, M.D., Pittsburgh.

Fatigue in Irritable Heart and Other Conditions. John T. Kipp, Jr., M.D., Baltimore.

Archives of Internal Medicine

VOL. 23 MAY, 1919 No. 5

CLINICAL SIGNIFICANCE OF BLOOD SUGAR IN NEPHRITIS AND OTHER DISEASES*

JOHN R. WILLIAMS, M.D.

WITH THE COLLABORATION OF

ELEANOR M. HUMPHREYS, B.S.†

ROCHESTER, N. Y.

First Paper

INTRODUCTION

Chemical examination of the blood is becoming more and more important in the clinical study of disease. Particularly is this true in those diseases in which the primary disturbance is one of perverted metabolism, of which diabetes mellitus and nephritis are the most common examples. The study of the sugar content of the blood in this field has attracted the attention of many workers, and there have appeared in the literature numerous contributions dealing with the significance of blood sugar and the various problems which it presents.

The studies thus far reported as to the clinical significance of blood sugar have been too few in number and too limited in character for the subject to be dismissed as one clearly elucidated. Moreover, certain methods of investigation have recently been proposed which appear to be worthy of statistical confirmation. For these reasons we propose in this study to present our observations and conclusions from a clinical study of blood sugar in a series of cases of diabetes, nephritis and other miscellaneous, but less important, disorders of body metabolism.

METHODS

In our studies on the sugar content of the blood, we have made use of the Myers[1] modification of the Lewis-Benedict[2] method for the determination of blood glucose. For the qualitative determination of urinary sugar, we have

* These studies were made in the Hahnemann Hospital, Rochester, N. Y., in which there is, under the direction of one of us, a hospital unit for the study of diseases of metabolism. This unit consists of a group of rooms in one ward and a well equipped special diet kitchen in charge of a trained dietitian. In conjunction with the hospital, there is a complete set of clinical and research laboratories, including a laboratory for work in pathologic chemistry.

† Working under the W. D. Ellwanger Fellowship in Pathological Chemistry.

1. Myers, V. C., and Bailey, C. V.: J. Biol. Chem. **24**:147, 1916.
2. Lewis, R. C., and Benedict, S. R.: J. Biol. Chem. **20**:61, 1915.

employed Benedict's[3] Qualitative Solution, and to quantitate, we have made use both of the polariscope and Benedict's[4] Quantitative Method.

The cholesterol determinations were made by Bloor's[5] method (Bloor II, so-called). The blood urea was determined by Van Slyke and Cullen's[6] modification of Marshall's urease method, while Folin's[7] method was employed in our creatinin investigations. Our uric acid determinations were made by the Benedict-Hitchcock[8] modification of the Folin-Macallum method, employing the technic recommended by Bogert.[9]

We used Van Slyke's[10] apparatus for measuring the carbon dioxid combining power of blood plasma, and determined the carbon dioxid content of the alveolar air by means of the Frederica apparatus. We employed the Tycos instrument in obtaining our blood pressure values.

STUDIES ON NORMALS

Normal Blood Sugar Values.—Many workers have studied this interesting problem and have obtained varying results. These variations can be accounted for partly because of the methods employed and partly because some of the supposed "normals" were not normal. This is particularly true in the early work on this subject. Strouse[11] states that there are no fixed normal values for blood sugar, but that these vary within certain limits with individual peculiarities and diet. Hopkins,[12] using the Bang micromethod, obtained figures ranging from 0.06 to 0.11 per cent. with an average of 0.085 per cent. He quotes the work of Bing and Jacobsen, using the same method, who noted normal values of from 0.06 to 0.12 per cent. Gettler and Baker[13] in their study of the blood in 30 normal individuals, employing the original Lewis-Benedict method, found the percentage of sugar varying from 0.05 to 0.11 per cent. Cummings and Piness,[14] using a modification of the Lewis-Benedict micromethod of analysis, obtained much lower values, ranging from 0.04 to 0.12 per cent., with an average of 0.07 per cent. Myers and Bailey[15] made observations on 500 cases, and state that most determinations made on individuals with no known cause for hyperglycemia show values from 0.09 to 0.11 per cent. and that a considerable number of hospital patients exhibit values from 0.12 to 0.14 per cent. Joslin[16] speaks of normal values between 0.06

3. Benedict, S. R.: J. Biol Chem. **5**:485, 1909.
4. Benedict, S. R.: J. Biol. Chem. **9**:57, 1911.
5. Bloor, W. R.: J. Biol. Chem. **24**:229, 1916
6. Van Slyke, D. D., and Cullen, G. E.: J. Biol. Chem. **19**:219, 1914.
7. Folin, O.: J. Biol. Chem. **17**:479, 1914.
8. Benedict, S. R., and Hitchcock, E. H.: J. Biol. Chem. **20**:619, 1915.
9. Bogert, L. J.: J. Biol Chem. **31**:165, 1917.
10. Van Slyke, D. D., Stillman, E., Cullen, G. E., and Fitz, R.: J. Biol. Chem. **30**:289, 1917.
11. Strouse, S.: Johns Hopkins Bull. **26**:214, 1915.
12. Hopkins, A. H.: Am. J. M. Sc. **149**:254, 1915.
13. Gettler, A. O., and Baker, W.: J. Biol. Chem. **25**:217, 1916.
14. Cummings, R., and Piness, G.: Arch. Int. Med. **19**:727, 1917.
15. Myers, V. C., and Bailey, C. V.: J. Biol. Chem. **24**:152, 1916.
16. Joslin, E. P.: Treatment of Diabetes Mellitus, 1917, p. 727.

and 0.11 per cent., with most observations about 0.10 per cent. Dennis, Aub and Minot[17] obtained values of from 0.85 to 0.11 per cent., using the Myers[1] modification of the Lewis-Benedict[2] method.

We also have endeavored to study the blood sugar values in normals. A series of thirty-nine young adults of both sexes in active life, who on careful physical and clinical examination appeared to be in good health, were selected for the blood-sugar tests. For purpose of emphasis, it may be said that all were urine sugar-free. The examinations were made at intervals of from one to six hours after the previous meal. The blood sugar values ranged from 0.07 to 0.15 per cent. In twenty-nine cases the values were 0.11 per cent. or less, while nine cases ranged from 0.12 to 0.14 per cent. One case had 0.15 per cent. The average of the series was 0.11 per cent. As a group there was no well marked relationship between the time of eating and the blood sugar level.

In addition to these, we have made observations on seventy-four other normals, the blood sugar values varying from 0.07 to 0.14 per cent., the average being 0.106 per cent. Thus we have examined in all, 113 normal individuals whose blood sugars averaged 0.107 per cent. Further, we have made blood sugar determinations on sixty miscellaneous cases not diabetes or nephritis, including gastro-intestinal disorders, pernicious anemia, etc. The range of values in these cases was from 0.07 to 0.16 per cent., with an average of 0.115 per cent. We have not sufficient data on any of these diseases to make an arbitrary statement as to the blood sugar findings, but it may be of interest that in four observations on two cases of cirrhosis of the liver, the readings were high normal or slightly elevated, varying from 0.12 to 0.16 per cent. In the light of Benedict and Lewis'[18] statement that the blood sugar is increased in cancer, in five out of ten observations on nine cases of carcinoma, we found a moderate elevation, 0.12 to 0.16 per cent. In a series of twenty-two cases of miscellaneous infections, the range was from 0.07 to 0.15 per cent., with an average of 0.11 per cent.

BLOOD SUGAR IN NEPHRITIS

A number of workers have studied the blood sugar in nephritis. Hopkins,[12] using Bang's micromethod, studied a series of twenty-six patients, many of whom were evidently seriously ill. The blood sugar was normal in only five cases. The others showed a definite but moderate hyperglycemia.

In sixteen cases with a systolic blood pressure ranging from 180 to 280 mm. the blood sugar was normal in only five cases. The others

17. Dennis, W., Aub, J. C., and Minot, A. S.: Arch. Int. Med. **20**:964, 1917.
18. Benedict, S. R., and Lewis, R. C.: Med. Rec. **77**:650, 1914.

showed a definite but moderate hyperglycemia. In ten cases without high blood pressures, seven had normal blood sugars and three showed hyperglycemia. In the series the blood sugar ranged from 0.06 to 0.159 per cent.

Myers and Bailey[1] report a series of 33 blood sugar observations on 11 cases of severe nephritis. In 21 observations on 7 cases of interstitial nephritis (all fatal but one) the blood sugar ranged from 0.10 to 0.22 per cent. There was no glycosuria in these cases. In 10 observations on 10 cases of the parenchymatous type, the blood sugar varied from 0.14 to 0.20 per cent. These cases exhibited a mild glycosuria. In their experience generally, high blood sugar accompanied high urea, though in one case of parenchymatous nephritis with a blood sugar ranging from 0.17 to 0.20 per cent., the blood urea values were well within the normal limits, 22 mg. and 30 mg. per 100 c.c.

Myers and Killian[19] in a report of twenty-three cases of nephritis state that the blood sugar values vary from 0.11 to 0.32 per cent., with an average of 0.157 per cent. They conclude that in general, high blood sugar values accompany high blood urea values.

Mason[20] states that the renal threshold is elevated in acute nephritis and reports that in one case after the ingestion of 100 gm. of glucose the blood sugar values in hourly periods were as follows: 0.10, 0.18, 0.217, 0.17 and 0.11 per cent. There was no urinary sugar.

We have studied in all 50 patients with cardiorenal disease, on whom we have made 88 blood sugar observations. The range of blood sugar levels was from 0.06 to 0.25 per cent., varying directly with the severity of the renal disease. Indeed, we are led to group our nephritis cases into three classes with reference to blood sugar content. In the early stages of interstitial or parenchymatous nephritis, when the general metabolism of the body is but little disturbed, blood sugars as a rule are normal. In the last stage of the disease, when the patient is in uremia, the blood sugar will be found very high, often equaling the blood sugar levels of severe diabetes. Other important metabolic constituents of the blood will also be found correspondingly increased, the whole presenting a picture of complete metabolic failure. A third group of cardiorenal cases, characterized by high blood pressure and little or no evidence of renal disturbance, usually exhibits high blood sugar levels. It is quite probable, as has been suggested by many workers, that some disturbance in the suprarenal bodies or other endocrinal glands is responsible both for the high blood pressure and the increased blood sugar. We were not able to throw light on this phase of the question. In general, it may be said

19. Myers, V. C., and Killian, J. A.: J. Biol. Chem. **29**:179, 1917.
20. Mason, E. H.: Arch. Int. Med. **21**:216, 1918.

that high blood sugar levels are associated with the severe phases of cardiorenal disease. These patients often excrete small quantities of sugar in the urine, although there appears to be no such quantitative relationship between food intake and urine sugar outgo as obtains in diabetes. Furthermore, the blood sugar level is inappreciably influenced by carbohydrate restriction in the diet. The practical significance of these facts is that such cases are often subjected to the discomfort of rigorous diabetic treatment, which is without effect either on the blood sugar level or the elimination of reducing substances in the urine.

TABLE 1.—COMPARISON OF BLOOD SUGAR LEVELS WITH OTHER CLINICAL DATA RELATING TO KIDNEY FUNCTION IN CASES OF CHRONIC DIFFUSE NEPHRITIS OF MILD AND MODERATE SEVERITY

No.	Sex	Age	Range of Blood Sugar, per Cent.	Range of Blood Pressure		Range of Blood Urea, Mg. per 100 C.c.	Phthalein Output, per Cent.	Ambard Coefficient
				Systolic	Diastolic			
1879	M	37	0.08-0.13	110-70	85-50	30-89	48	
2196	M	59	0.09-0.13	160-150	90	57-106	25	0.301
2270	M	30	0.10	180	120	86		
2438	M	52	0.11	160	100	118-123	25	0.401
2064	F	42	0.11	200	110	74		
2179	M	74	0.08	175	90	41		
2419	M	24	0.10	156-170	110-120	42-58	....	0.255
2220	M	13	0.10	115	80	50-77	....	0.137

TABLE 2.—COMPARISON OF BLOOD SUGAR LEVELS WITH OTHER CLINICAL DATA RELATING TO KIDNEY FUNCTION IN CASES OF CHRONIC DIFFUSE NEPHRITIS OF SEVERE TYPE

No.	Sex	Age	Range of Blood Sugar, per Cent.	Range of Blood Pressure		Range of Blood Urea, Mg. per 100 C.c.	Phthalein Output, per Cent.	Ambard Coefficient	Outcome
				Systolic	Diastolic				
1946	F	50	0.09-0.25	140-210	80-110	99-461	2.5-15	0.13	Dead
2143	F	46	0.13-0.20	180-240	100-140	188-277	3	0.68-2	Dead
2152	M	25	0.09-0.12	145-220	100-180	55-228	....	0.29-0.19	Dead
2156*	M	25	0.08-0.15	210-220	160-190	81-255	....	.....	Dead
2243	M	45	0.18-0.20	170-180	90-105	353-492	....	.....	Dead
2144	M	34	0.12-0.18	225	125	114-242	....	0.68	Dead
1690	M	54	0.14	130-180	70-130	894	7-10	.....	Dead
WC1	F	56	0.22	.....	.....	270	....	.....	Dead
WC2	M	55	0.14	.....	.....	132-196	....	0.49	?

* This case separately discussed. † Nonprotein nitrogen.

These patients (Table 1) were mildly sick clinically. It will be noted that the blood ureas and the Ambard coefficients of urea concentration are but moderately increased. Blood pressures, both systolic and diastolic, do not indicate a very serious disturbance. Blood sugar levels in each instance are normal. Disturbance in nitrogen metabolism precedes the rise in blood sugar.

These patients (Table 2) were all critically ill. In some instances the observations were made in the terminal stage of the disease. The high blood pressures, the severe albuminuria, extreme nitrogen reten-

tion, two-hour renal studies, high Ambard coefficients, etc., all indicate serious impairment of kidney function. In each of these cases the failure in nitrogen metabolism preceded the rise in the blood sugar level, the latter only becoming high in the critical stage of the nephritis.

These cases (Table 3) were all characterized by severe general edema, severe albuminuria, normal or moderately elevated blood pressures, little or no evidence of nitrogen retention and normal blood sugars. The high blood sugar determinations in cases 1669, 1960 and 1816 were obtained when the patients were moribund and probably represent terminal failure of metabolism.

TABLE 3.—Comparison of Blood Sugar Levels with Other Clinical Data Relating to Kidney Function in a Series of Chronic Parenchymatous Nephritis of the Severe Type

No.	Sex	Age	Range of Blood Sugar, per Cent.	Range of Blood Pressure		Range of Blood Urea, Mg. per 100 C.c.	Phthalein Output, per Cent.	Outcome
				Systolic	Diastolic			
2460	M	40	0.11	140-170	120-130	30-83	....	Dead
2226	F	22	0.11-0.11	150	100-105	39-85	59	Living
1669	M	59	0.14	180-225	100-130	67	23-55	Dead
2298	M	17	0.10-0.10	138	80	38-128	58	Living
2266	F	39	0.11	110-150	85-90	21-46	28	Living
1960	F	67	0.08-0.18	140-150	80	41-95	12	Dead
1816	M	54	0.13-0.20	210-240	130-160	64-92	22	Dead

TABLE 4.—Comparison of Blood Sugar Levels with Other Clinical Data Relating to Kidney Function in a Series of Cases of Cardiovascular Disease

No.	Sex	Age	Range of Blood Sugar, per Cent.	Range of Blood Pressure		Range of Blood Urea, Mg. per 100 C.c.	Phthalein Output, per Cent.	Outcome
				Systolic	Diastolic			
2110	F	52	0.12	200	100	45	....	Living
2170	F	73	0.16	160-200	85-100	38	....	Living
1829	M	51	0.12	170-200	100-120	40	41	Living
1853	F	56	0.11	200-240	110-120	31-40	....	Living
2263	M	44	0.12-0.13	180-210	110-140	30-43	....	Living
1429	M	51	0.11	180-220	120-150	40-56	22-30	Dead
2176	M	53	0.10-0.15	150-180	120	23-61	....	Dead
2358	F	54	0.11	200-220	130-140	40-77	23	Living
2308	M	48	0.11	200-230	140-170	37-79	14-13	Living
2154	M	63	0.10	160-180	80-100	31-45	....	Living
1988	F	60	0.10	.....	.....	68	35	Living
2225	M	66	0.10	190-240	.....	53	....	Living
1633	F	49	0.12	140-190	100-120	34	46-70	Living
2440	F	54	0.12-0.23	170-220	115-140	43-19	46-70	Living
2185	M	53	0.20	160	90-110	41-51	43	Living

These cases (Table 4) are characterized by very severe hypertension, slight or no albuminuria, and little or no nitrogen retention. They all exhibit normal blood sugars except case 2176, in which the high observation was made when the patient was moribund, and cases 2170, 2185 and 2440, whom we believe from other clinical evidence to have some endocrinal disturbance. Case 2440 we have studied in detail. Clinically, Cases 2110, 2263, 1829 and 1633 seem to be in the early stages of this same endocrinal type.

TABLE 5.—CASE 1946. COMPARATIVE BLOOD ANALYSES IN A FATAL CASE OF CHRONIC DIFFUSE NEPHRITIS IN THE BEGINNING AND TERMINAL STAGES

Date 1917	Blood Analysis					Urine Analysis		Diet			
	Urea, Mg. per 100 C.c.	Creatinin, Mg. per 100 C.c.	Cholesterol, Mg. per 100 C.c.	Ambard Coefficient	Sugar, per Cent.	Sugar	Albumin	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories
6/12 1918	99.4	10.2	180	0.13	0.09	0	+++	30	77	137	1,471
4/11	348.9	10.0	....	.....	0.15	0	++	33	22	74	680
4/12	323.2	11.1	198	.....	0.25	0	++	33	22	74	680
4/13	400.5	16.1	....	.....	0.25	0	0	33	22	74	680

CASE 1 (No. 1946).—Woman, aged 50; nephritis, probably of less than one year's duration. Blood pressure at time of first examination, systolic 150 mm., diastolic 90 mm. Clinical symptoms at first comparatively mild with moderate elevation of blood urea and normal blood sugar. High blood creatinin portended fatal outcome. The blood analyses made ten months later and just before death reveal a severe failure of nitrogen metabolism and an accompanying rise in blood sugar. It is noteworthy that nitrogen retention preceded the failure in sugar metabolism. The patient's urine was sugar-free. The renal blood sugar threshold in this case was more than 0.25 per cent. (Table 5).

TABLE 6.—CASE 2144. COMPARATIVE BLOOD ANALYSES IN A SEVERE CASE OF CHRONIC DIFFUSE NEPHRITIS

Date 1917	Blood Analysis						Urine Analysis		Diet			
	Urea, Mg. per 100 C.c.	Creatinin, Mg. per 100 C.c.	Cholesterol, Mg. per 100 C.c.	Ambard Coefficient	Blood Plasma CO_2, C.c. per 100 C.c.	Sugar, per Cent.	Sugar	Albumin	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories
9/17	242.0	8.8	128	.....	40.9	0.18	0	+++	32	32	64	640
9/25	114.2	10.6	160	0.08	30.0	0.14	0	+++	38	38	76	760
9/27	.....	12.2	...	.....	20.0	0.12	0	+++	32	32	64	640

CASE 2 (No. 2144).—Man, aged 34; nephritis of seven years' standing. Blood pressure, systolic 225 mm., diastolic 120 mm. On admission to hospital there was severe general edema and dyspnea. Blood examinations showed evidence of extreme metabolic failure in the high urea and sugar. High creatinin and low plasma carbon dioxid portended fatal outcome. On Karrell diet, noteworthy clinical improvement with disappearance of edema and dyspnea accompanied by a sharp decline in blood urea and sugar. Patient left hospital in good condition but succumbed to pneumonia one month later (Table 6).

CASE 3 (No. 1816).—Man, aged 54; clinical evidence of severe arteriosclerosis over a period of two years. Blood pressure, systolic ranging from 220 to 250 mm., diastolic 110 to 140 mm. Data in Table 7 represents the terminal stage of the disease. Attention is called to the slight nitrogen retention and the slightly elevated blood sugars. At the time of the last test, the patient was critically ill, edema and dyspnea were very pronounced. This case illustrates the probable degree of metabolic failure in the terminal stage of chronic parenchymatous nephritis.

CASE 4 (No. 2156).—Man, aged 25; had been a chronic alcoholic for eight years; admitted to hospital in delirium and coma two weeks before death. Blood pressure, systolic 210 mm., diastolic 160 to 190 mm. Note (Table 8) the comparatively slight failure of nitrogen metabolism on admission and the rapid change to a condition of marked retention before death. These findings are paralleled by the blood sugar curve. The absence of severe acidosis as

shown by the blood plasma curve is noteworthy in this case. Necropsy findings: The kidneys presented very little gross evidence of disease. On section there was a moderate degree of connective tissue in the cortex, some sclerosis of the blood vessels and a little patchy calcification in the tubules. The medullary rays were but a little affected. The brain was extremely edematous and hemorrhagic.

TABLE 7.—Case 1816. Comparative Blood Analyses in a Patient who, in the Early Stages of This Study, Presented Clinical Evidence of General Arteriosclerosis and Renal Sclerosis, Later Developing Signs of Parenchymatous Nephritis with Severe Albuminuria and Edema and Slight Nitrogen Retention. Fatal Termination Three Months after Last Analysis

	Blood Analysis						Urine Analysis		Diet			
Date 1917	Urea, Mg. per 100 C.c.	Creatinin, Mg. per 100 C.c.	Uric Acid, Mg. per 100 C.c.	Ambard Coefficient	Blood Plasma CO_2, C.c. per 100 C.c.	Sugar, per Cent.	Sugar	Albumin	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories
10/16	67.21	4.2	.....	0.24	48.1	0.14	0	+++	32	32	64	640
10/25	65.78	3.6	7.97	.....	53.2	0.14	0	+++	39	38	134	1,031
11/ 5	64.64	2.5	6.90	.....	.....	0.13	0	+++	67	75	136	1,176
11/19	92.95	....	.....	.....	50.9	0.20	0	+++	61	126	225	2,292

TABLE 8.—Case 2156. Comparative Blood Analyses in a Fatal Case of Chronic Alcoholism and Chronic Diffuse Nephritis

	Blood Analysis						Urine Analysis		Diet			
Date 1917	Urea, Mg. per 100 C.c.	Creatinin, Mg. per 100 C.c.	Uric Acid, Mg. per 100 C.c.	Cholesterol, Mg. per 100 C.c.	Blood Plasma CO_2, C.c. per 100 C.c.	Sugar, per Cent.	Sugar	Albumin	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories
10/16	80.8	2.8	.....	192	52.8	0.08	0	++++	16	16	32	320
10/19	82.9	3.7	.....	.....	48.1	0.10	0	++++	25	25	68	580
10/24	254.5	6.2	13.0	.....	50.3	0.15	0	++++	6	0	0	30
10/27	230.2	7.0	.....	.....	50.5	0.15	0	+	5	2	19	99

TABLE 9.—Case 2143. Comparative Blood Analyses in the Terminal Stages of a Fatal Case of Chronic Diffuse Nephritis

	Blood Analysis							Urine Analysis		Diet			
Date 1917	Urea, Mg. per 100 C.c.	Creatinin, Mg. per 100 C.c.	Uric Acid, Mg. per 100 C.c.	Cholesterol, Mg. per 100 C.c.	Ambard Coefficient	Blood Plasma CO_2, C.c. per 100 C.c.	Sugar, per Cent.	Sugar	Albumin	Protein, Gm.	Fat, Gm.	Carbohydrate, Gm.	Calories
9/29	186.8	6.2	....	...	....	38.5	0.14	0	+++	32	32	64	640
10/ 3	.....	9.1	11.2	240	....	32.3	0.16	0	++	32	32	64	640
10/ 4	140.1	8.9	11.5	...	0.68	34.3	0.13	0	++	32	32	64	640
10/11	231.7	12.9	13.2	201	1.90	29.1	0.19	0	+++	39	37	107	903
10/19	277.4	12.8	....	...	....	24.1	0.20	0	++++	2	1	54	436

Case 5 (No. 2143).—Woman, aged 46; blood pressure, systolic 230 mm., diastolic 140 mm.; extensive edema; severe dyspnea. The failure of nitrogen metabolism (Table 9) was more serious and preceded the failure in sugar metabolism. High renal blood sugar threshold. Necropsy findings: kidneys, gross examination, small, contracted. On section the cortex exhibited an extreme degree of fibrosis and granulation tissue which had obliterated a

generous percentage of the parenchymatous structures. Many of the glomeruli were scarred while those remaining had a varying degree of sclerosis in the tufts. The dilated convoluted tubules contained degenerate necrotic epithelium. The blood vessels showed an extreme grade of hyaline necrosis, particularly in the intima, almost to the point of obliteration. Marked cloudy swelling and fatty degeneration of the liver and suprarenal bodies were present.

CONCLUSIONS

1. The average digestion blood sugar level in 113 normal individuals was 0.107 per cent., the values ranging from 0.07 to 0.14 per cent.

2. The range of the blood sugar level in a series of sixty cases of miscellaneous diseases, chiefly gastro-intestinal disorders and pernicious anemia, excluding diabetes, nephritis and infections, was from 0.07 to 0.16 per cent., with an average of 0.115 per cent.

3. In a series of nine cases of carcinoma there was a moderate elevation of blood sugar, 0.12 to 0.16 per cent.

4. In a series of twenty-two miscellaneous infections, chiefly influenza, pneumonia, and streptococcus, the range was from 0.07 to 0.15 per cent., with an average of 0.11 per cent.

5. In the early stages of nephritis, when the general metabolism of the body is but little disturbed, blood sugars, as a rule, are normal.

6. In the last stages of nephritis, when the patient is in uremia, the blood sugar will be found very high, often equalling the severe stages of diabetes. Other important metabolic constituents of the blood will be found correspondingly increased, presenting a picture of complete metabolic failure.

7. A third group of cardiovascular cases, characterized by high blood pressure and little or no evidence of renal disturbance, usually exhibits blood sugar levels slightly higher than normal.

8. In severe cases of nephritis, patients may excrete small quantities of sugar in the urine, frequently giving rise to the misapprehension that true diabetes exists. In such cases the blood sugar level is inappreciably influenced by carbohydrate restriction, and these patients should not be subjected to the discomfort of rigorous diabetic diet.

9. Failure in nitrogen metabolism precedes, often by months, the rise in blood sugar, so that the latter has a rather serious prognostic omen.

388 Monroe Avenue.

THE CLINICAL SIGNIFICANCE OF BLOOD SUGAR IN DIABETES MELLITUS

JOHN R. WILLIAMS, M.D.
WITH THE COLLABORATION OF
ELEANOR M. HUMPHREYS, B.S.
ROCHESTER, N. Y.

Second Paper

We have studied the blood sugar levels in 127 cases of diabetes, fifty-six males and seventy-one females, making in all 1,106 blood sugar determinations. In our study of the renal threshold for sugar in diabetes, we found no constant blood sugar level for the appearance of urinary sugar. Hopkins[1] says that there is no constant renal threshold. Hamman and Hirschman[2] found the normal threshold between 0.17 and 0.18 per cent., and our own findings would seem to corroborate this. In diabetes, however, we may find a lowering or an elevation of the threshold. In the former case, the blood sugar level may be very slightly lowered or may approximate normal values. We now have under observation several patients who persistently show reducing substances in the urine accompanied by low blood sugar values. Some of these cases may prove to be cases of alimentary glycosuria or renal diabetes. We cannot say in diabetes whether the threshold remains the same for any length of time. We are sure, on the other hand, that it may vary widely with changes in the condition of the patient. We have noted an elevation of blood sugar in cases of diabetes complicated by nephritis, and particularly in certain diabetics, who, from mild or moderately severe stages of the disease, have developed into that more serious stage accompanied by acidosis and frequently by cholesterinemia. These cases are characterized by high blood sugar levels as will be shown presently.

It is important at this time to distinguish between blood sugar level and renal threshold since both expressions are used frequently throughout this paper. A diabetic on a very liberal diet may have a high percentage of sugar in his blood and at the same time be eliminating large amounts of sugar in his urine. The height of the blood sugar level at which he ceases to eliminate appreciable quantities of glucose is considered his renal threshold for sugar. This figure may be considerably below his highest blood sugar level. Thus, in one of our cases, the patient on admission to the hospital had a blood sugar level of 0.67 per cent., but his threshold later proved to be 0.17 per cent.

1. Hopkins, A. H.: Am. J. M. Sc. **149**:254, 1915.
2. Hamman, L., and Hirschman, I. I.: Arch. Int. Med. **20**:761, 1917.

We have attempted to study the effect of the duration of the diabetes on the renal threshold. The analysis of this study is seen in Table 1, in which the total number of cases showing different approximate threshold percentages is given.

TABLE 1.—SHOWING EFFECT OF DURATION OF DIABETES ON RENAL THESHOLD FOR SUGAR

Duration of Disease, Years	Blood Sugar Renal Threshold, per Cent.					Total Number of Cases
	0.15	0.17	0.19	0.24	0.25	
Less than 1	2	1	6	5	..	14
1 to 2	2	..	8	4	..	14
2 to 3	..	1	4	6	..	11
3 to 5	1	2	4	2	1	10
5 to 10	..	1	3	5	1	10
10 to 15	..	1	2	2	..	5
15	..	..	..	..	1	1
Total number of cases	5	6	27	24	3	65

In Table 1 it will be seen that two patients who had diabetes for less than one year had thresholds under 0.15 per cent. Six cases with diabetes of less than one year's standing had thresholds of less than 0.19 per cent., but more than 0.17 per cent., and so on. A cursory examination of the foregoing data leads one to the impression that there is no striking relation between the duration of the disease and the height of the renal blood sugar threshold. We feel, therefore, that this data should be interpreted in the light of our clinical experience. These studies are based on observations made in the hospital over a period averaging four weeks. Some few cases which were under observation for longer periods showed a comparatively rapid rise in threshold. Apparently when diabetes is mild or quiescent, the blood sugar threshold is stationary, but when the disease becomes progressive, the threshold tends to rise. Indeed, before death the blood sugar threshold may reach great heights with little or no sugar appearing in the urine. A rising renal threshold for sugar, therefore, in the face of careful dietary treatment, is a serious prognostic sign.

We have had an opportunity to study several cases illustrating this point and will cite three.

CASE 1.—Woman, aged 28. Fatal diabetes; under observation five months; early blood sugar renal thresholds 0.16 and 0.18 per cent.; in terminal stages, 0.20, and 0.25 per cent.

CASE 2.—Woman, aged 18. Fatal diabetes; under observation two and one-half years; early blood sugar renal thresholds 0.19 and 0.20 per cent.; in terminal stage, blood sugar thresholds 0.25 and 0.30 per cent.

CASE 3.—Woman, aged 22; severe diabetes; living; under observation six months; early thresholds below 0.18 per cent.; present threshold 0.20 and 0.25 per cent.; declining food tolerance.

The severity of the diabetes is therefore important in any consideration of blood sugar renal threshold. High thresholds are rarely seen in mild diabetes. When present, they usually mean some complications, as arterial hypertension. It is difficult to determine the threshold in mild cases, as a rule, because they yield readily to treatment and the opportunity for sufficient observations is not afforded. High thresholds are often found in mild cases in which the patients are on unrestricted diets. When a high threshold is found in mild uncomplicated diabetes, it is usually because the patient is eating very liberal diets, whereas in severe diabetes with a high threshold, the diet is usually low. The high threshold may mean a physiologic expedient to conserve food material. Mosenthal[3] expressed the view that a high blood sugar was a protective measure, but our experience indicates that persistent high blood sugar levels promote exhaustion and rapid decline of function, and the high threshold is merely a safety measure. Furthermore, in severe cases where extremely low diets are necessary to maintain life, the high threshold is essential to take care of the seriously impaired carbohydrate metabolism. Our experience has led us to the conclusion that it is desirable to maintain the blood sugar level as nearly normal as possible even though severe restrictions in diet may be necessary for this purpose, notwithstanding the fact that in most cases the high threshold will permit of a much more liberal diet without the appearance of sugar in the urine. We regard this as the cardinal feature in the successful treatment of diabetes, and look with misgiving and apprehension on any plan of treatment which permits of food just short of the point of glycosuria.

TABLE 2.—Relation of Blood Sugar Renal Threshold and Severity of Diabetes

Degree of Severity	Blood Sugar Renal Threshold, per Cent.					Total Number of Cases
	0.15	0.17	0.19	0.24	0.25	
Mild	2	2	7	8	..	19
Moderately severe	3	1	2	8	2	16
Severe	1	3	15	12	3	34
Total number of cases	6	6	24	28	5	69

It is our practice to make blood sugar determinations with every change in diet, and at least as often as every three days.

An analysis of sixty-nine cases of diabetes arranged to show the relation of blood sugar renal threshold and the severity of diabetes will be found in Table 2.

The age of the patient is undoubtedly a factor in the determination of the renal blood sugar threshold. Younger diabetics as a rule

3. Mosenthal, H. O., Clausen, S. W., Hiller, A.: Arch. Int. Med. **21**:93, 1918.

have low or normal thresholds. As age advances, the threshold rises. This may partly be explained by the frequently occurring complications of renal and endocranial involvement (Table 3).

TABLE 3.—AGE AND RENAL BLOOD SUGAR THRESHOLD

Age, Years	Blood Sugar Renal Threshold, per Cent.					Total Number of Cases
	0.15	0.17	0.19	0.24	0.25	
1 to 9	1	2	2	..	..	5
10 to 19	1	1	4	2	..	8
20 to 29	..	..	7	3	..	10
30 to 39	1	2	4	3	..	10
40 to 49	1	1	3	4	3	12
50 to 59	..	..	4	8	..	12
60 to 69	..	..	2	3	..	5
70 to 79	..	..	1	2	..	3
Total number of cases	4	6	27	25	3	65

INTERPRETATION OF CHARTS

The accompanying charts are plotted to show the relation of the height of blood sugar to other important clinical phenomena of diabetes, and especially to the severity of the disease. In general, the charts show the relation of food intake, body weight, carbon dioxid tension of alveolar air, blood sugar per cent., and urine sugar outgo. It will be noted that the food intake is plotted in calories, the key on the left border revealing the meaning of the different types of hatching. Food intake is thus plotted because the different elements of the diet are additive and the total intake as well as proportions of the various elements may thus be determined at a glance. The carbon dioxid tension of the alveolar air is plotted as the index to acidosis, although in the studies frequent determinations of the blood plasma carbon dioxid have been made as controls, using Van Slyke's[4] well known method. Readings below the line marked "normal minimum" indicate acidosis. Blood sugar is plotted in terms of per cent. It is assumed that above 0.15 per cent. is abnormally high; thus this line for purpose of ease in study is made bold faced. Urine sugar outgo is plotted in calories so that the carbohydrate balance of a case may be ascertained by comparing intake with outgo.

Chart 1.—Case 1936. Before admission to the hospital this little boy was examined by the authors and found to have 6.6 per cent. of sugar in the urine. He also presented the usual clinical symptoms of diabetes, as thirst, polyuria, weakness, and loss of weight. Except on occasions when he has had some infection, his blood sugar has remained remarkably low. Thus, when the test was made, Oct. 16, 1917, he had a severe bronchitis. The test on Dec. 5, 1918, was made three days after the removal of the tonsils. This child is

4. Van Slyke, D. D., Stillman, E., Cullen, G. E., and Fitz, R.: J. Biol. Chem. **30**:289, 1917.

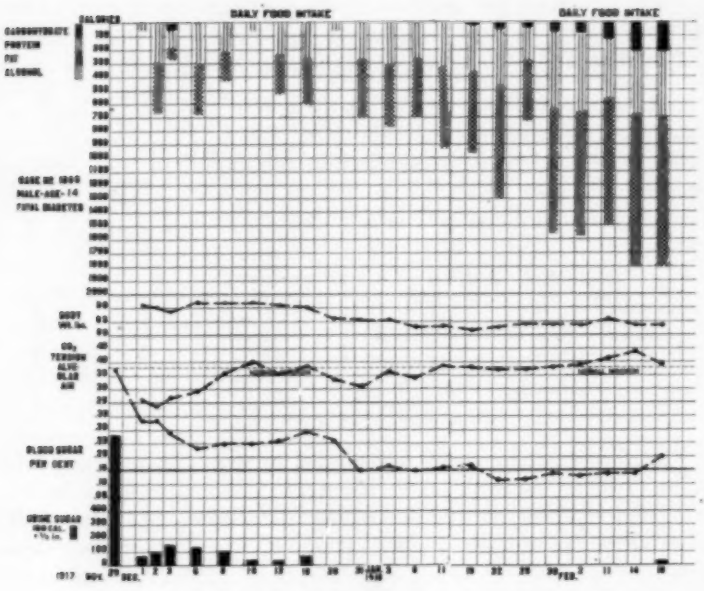


Chart 1

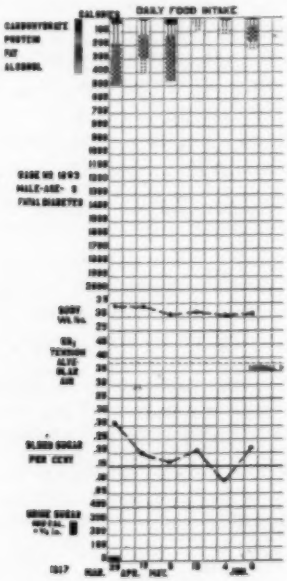


Chart 2

growing slowly and gaining weight steadily. The lowness of his blood sugar curve attests to the mildness of his diabetes and his response to treatment. In our experience, a persistent low blood sugar curve in a child is an extremely favorable prognostic sign.

Chart 2.—Case 1883. This little 5-year-old child first presented symptoms of diabetes about one month before entering the hospital. He was under continuous observation for sixteen weeks. It was quite impossible to keep him urine sugar-free on the most rigorous diets. Only a portion of his metabolism record is here shown. It was noteworthy that he had a persistent high blood sugar curve and an absence of acidosis except at the end. Acidosis in this case was measured by urinary ammonia output and is not here shown. In the favorable cases in children which we have studied, blood sugar levels are usually low.

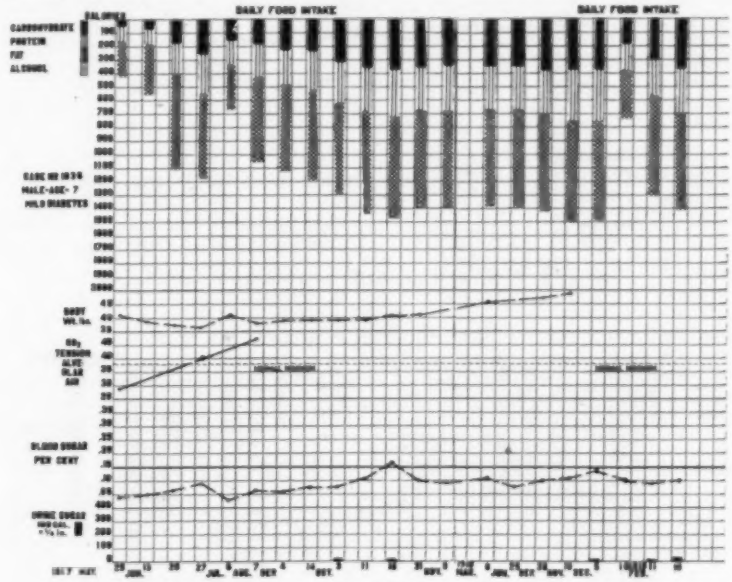


Chart 3

Chart 3.—Case 1660. This boy had severe diabetes for more than two and one-half years. When admitted to the hospital he was in extreme acidosis and had a very high blood sugar, as will be observed. He also had a very high blood cholesterol. It was with great difficulty that his blood sugar level was reduced, this being accomplished by alternating fasting and underfeeding. He was finally discharged in good condition and on a fairly liberal diet. A few months later he committed excesses in eating and rapidly succumbed in coma.

Chart 4.—Case 2288. This patient has had severe diabetes for the past four years. She is emaciated and presents the usual clinical picture of an individual who has undergone prolonged undernourishment. On admission to the hospital and while on a very low diet, she had a persistent high blood sugar which was difficult to reduce; but by persistent underfeeding and particularly by keeping the carbohydrate intake low, usually less than 10 gm., and

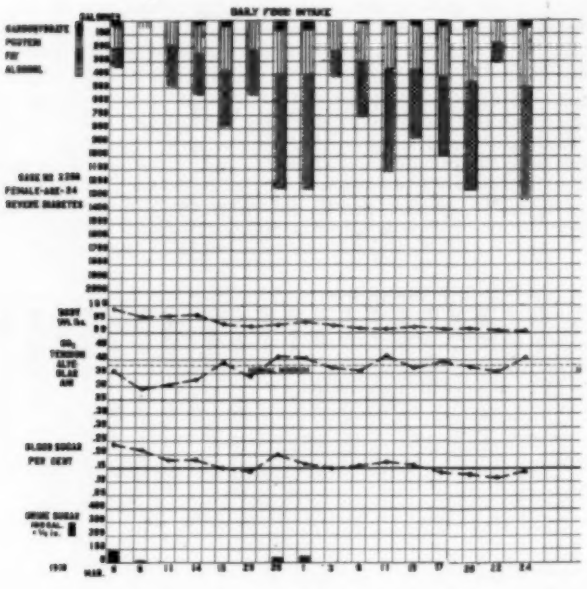


Chart 4

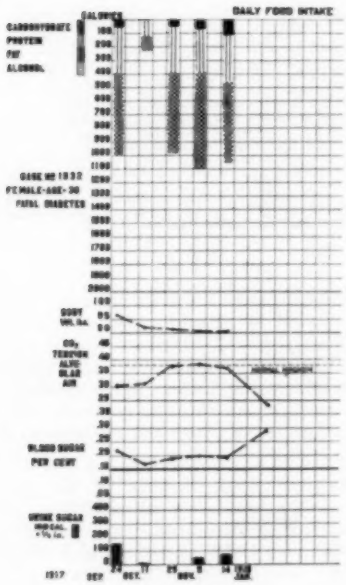


Chart 5

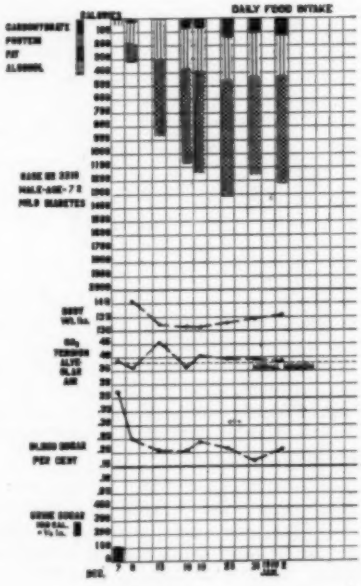


Chart 6

often none, her blood sugar level was reduced to between 0.12 and 0.15 per cent. The patient has remained on this low diet for more than one year and is doing fairly well.

Chart 5.—Case 1532. This patient first came under observation in September, 1915, shortly after the onset of her diabetes. For the first few months, there was no difficulty in keeping her urine sugar-free although she was on a diet containing upwards of 2,300 calories. The patient was then being fed liberally of fat, which probably was a serious mistake. During the whole year 1916 great difficulty was experienced in keeping her urine sugar-free for any length of time. Frequent rest days were necessary for that purpose. The first blood sugar determination was made March 10, 1916, and was 0.17 per cent. Routine blood sugar examinations were not begun until September, 1917. It is quite probable, however, that the patient had a high level all of the time, for traces of sugar were frequently appearing in the urine, indicating that the food intake kept the blood sugar level up to the point of the threshold. The data shown in the chart is taken at random from the patient's record and is characteristic of the course of her metabolism. As in the other severe cases shown in this study, it was quite impossible to reduce the blood sugar level to anything approximating normal by fasting or underfeeding. Until a few days before death, which was induced by a severe cold, there was no appreciable evidence of acidosis.

Chart 6.—Case 2218. Mild diabetes associated with advanced arteriosclerosis and chronic interstitial nephritis. The kidney lesion in this case was much more serious than the diabetes and it is not improbable that the high blood sugar curve is thus explained.

Chart 7.—Case 2184. This patient has had diabetes for more than eight years. One month before admission to the hospital a perforating ulcer developed on one foot. In a short time this foot had become gangrenous so that on November 22 it was thought wise to amputate the leg below the knee. The wound healed slowly, several gangrenous sloughs developing, so that during the entire hospital stay the wound remained open and infected, although gradually improving. Ultimately it healed and the patient made a good recovery so that he is sugar-free on a liberal diet. The persistent high blood sugar in this case is undoubtedly induced by the gangrene.

Chart 8.—Case 2122. This patient was admitted to the hospital with severe moist gangrene of one foot. Her failure of metabolism became more and more pronounced, acidosis becoming increasingly severe each day up to the time of death, Oct. 22, 1917. Attention is called to the persistent high blood sugar curve in this case, in spite of the low diet. We have studied several cases of this type and have observed that the blood sugar curve remains high in the presence of severe infection and gangrene.

Chart 9.—Case 1680. This young woman had severe diabetes for about two and one-half years before she finally succumbed. During that time she was in the hospital for observation several times, staying several weeks each time. She was unusually faithful and closely cooperated in the study. This patient had a high degree of cholesterinemia, but up to a short time before death there was an absence of acidosis notwithstanding the low diet. It was quite impossible to get her blood sugar down to the normal limits, even with the most rigorous treatment. Weeks of total abstinence from carbohydrates, even excluding thrice cooked vegetables, did not suffice. The dextrose nitrogen ratio at the time of the last observation was 5.11. This patient well illustrates the point that cases presenting intractably high blood sugars have an ominous prognosis.

Chart 10.—Case 2115. This young woman had severe diabetes for about two years before coming under observation. When admitted to the hospital she presented the usual clinical evidences of severe diabetes. It was quite

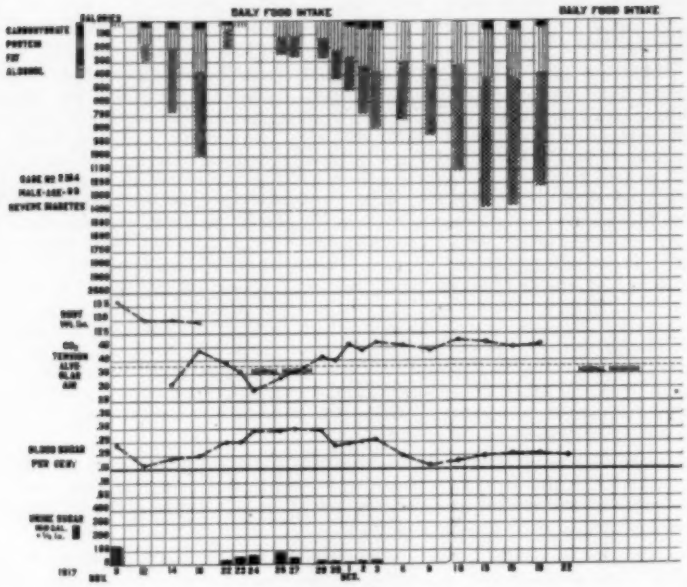


Chart 7

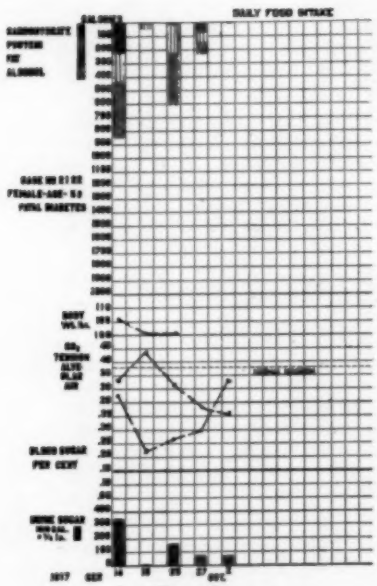


Chart 8

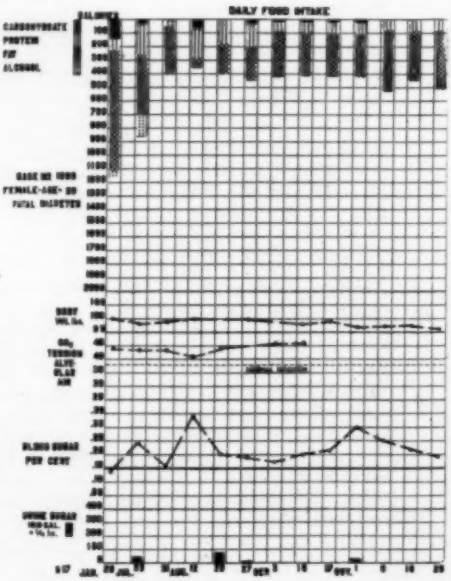


Chart 9

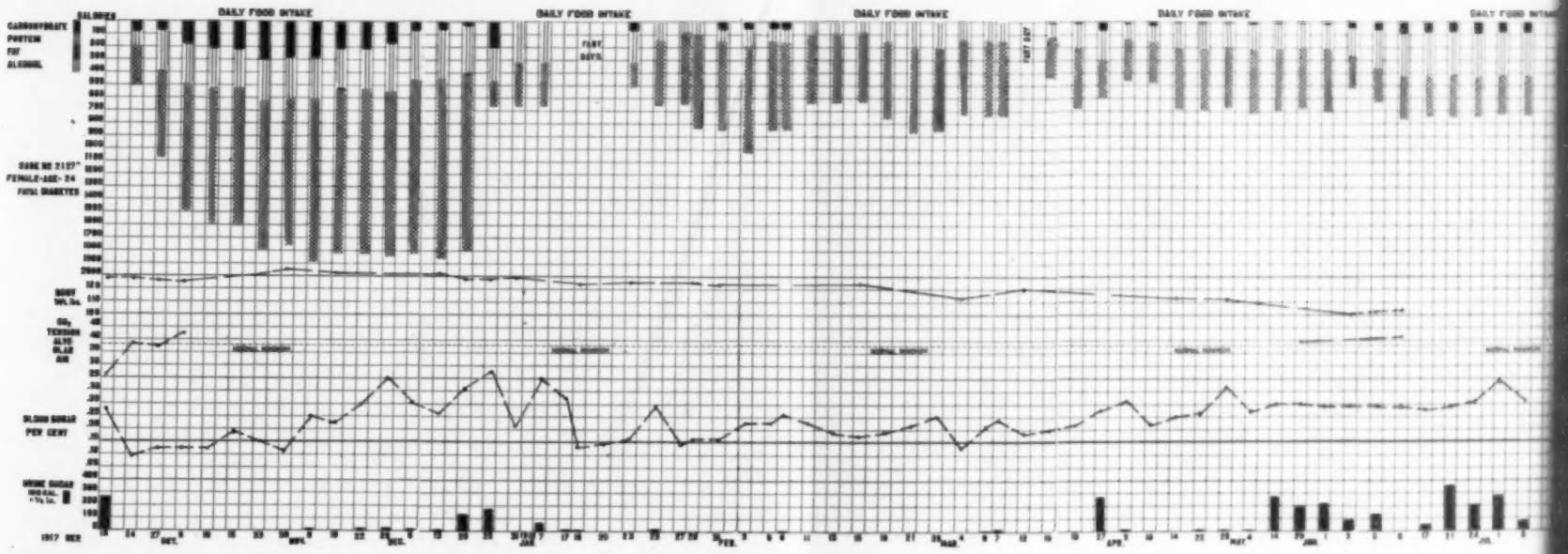

DAILY FOOD INTAKE
DAILY FOOD INTAKE
DAILY FOOD INTAKE
DAILY FOOD INTAKE
CASE NO 2127
FEMALE-AGE- 24
FATAL DIABETES
1917 DEC
NOV.
DEC.
JAN.
FEB.
MAR.
APR.
MAY.
JUN.
JUL.

Chart 11

impossible, even on very low diets, to reduce her blood sugar level to normal limits. She was accordingly a very discouraging case for treatment. The very high blood sugar levels and large urinary sugar outgo at the end are probably explained by the fact that the patient ate surreptitiously other food than the prescribed diet.

Chart 11.—Case 2127. This case is of interest and importance to the student of diabetes because it illustrates the serious difficulties which are occasionally encountered in attempting to control the disease. The patient was an intelligent, cheerful young woman who cooperated most carefully in this study. When admitted to the hospital, Sept. 19, 1917, she was in a severe state of acidosis, her urine contained more than 7 per cent. of sugar, and she had a chronic middle ear disease which received expert attention. For

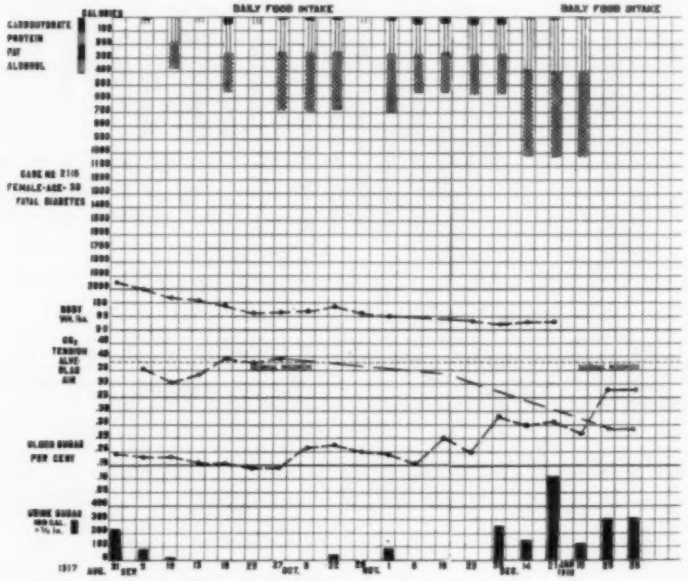


Chart 10

a few weeks she did very well and was given a diet of upwards of 1,800 calories, which included between 145 and 150 gm. of fat. On this diet traces of sugar appeared in the urine and there was a marked elevation in blood sugar which for a few weeks was disregarded. Dec. 20, 1917, approximately three months after the discovery of the diabetes, the attempt was begun by fasting, undernutrition, and by feeding carbohydrate-free diets to reduce the blood sugar to normal. Beginning Jan. 15, 1918, and for five days, the patient was given absolutely no food. This reduced the blood sugar to 0.13 per cent. For the next five days less than 500 calories of food per day were allowed, yet the blood sugar went up to 0.17 per cent. Thereafter, for the next six months, the diet was rarely permitted to get above 800 calories, often it was much below this, yet in spite of this continued and prolonged underfeeding, the blood sugar maintained a high level, ranging from 0.20 to 0.40 per cent. It will be observed that the point where sugar appeared in the urine or the renal threshold, was well above 0.20 per cent. from the beginning.

It is the experience of the writers that when a patient presents such a persistent and unyielding blood sugar curve as is exhibited by this case, the prognosis is very bad and the termination of the disease in death close at hand.

Chart 12.—Case 2253. Diabetes was first discovered in this patient Jan. 1, 1917. One year later a small hard mass of granulation tissue formed under the nail of the right great toe. From this, there oozed a thin, watery discharge. At the time the patient came under the observation of the writers, Jan. 23, 1918, she was not in good condition, having just undergone a month's fasting and underfeeding in another hospital. She was then fasted, kept on a carbohydrate-free diet and underfed for two weeks without appreciable effect on her blood sugar level. The granulomatous mass was removed, Feb. 6, 1918, by Dr. W. I. Dean. Following the operation there was immediate decline in the blood sugar level and with it an increase in food tolerance and note-

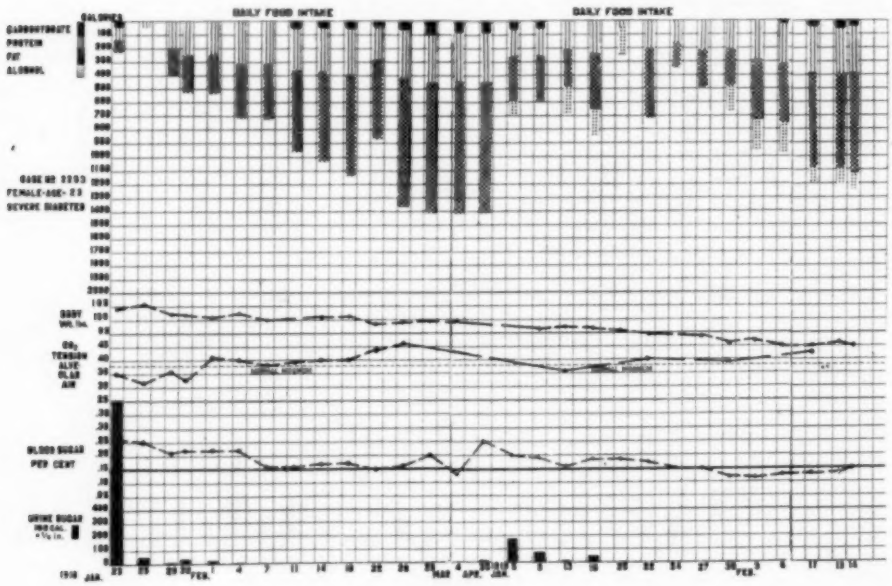


Chart 12

worthy clinical improvement. The patient left the hospital March 4, 1918, on a diet that was probably a little too high. She did very well for several months and then became careless in eating. She returned to the hospital, Jan. 5, 1919, with a blood sugar of 0.20 per cent. She was then kept on a very low carbohydrate-free diet, averaging less than 600 calories, for nearly a month. During this time there was a gradual decline in the blood sugar level to approximately 0.12 per cent and a material clinical improvement. It will be noted that alcohol has been used in this case. From observations on a number of intractable cases of diabetes with high blood sugar, the writers are inclined to the view that small quantities of alcohol are of value in promoting carbohydrate metabolism.

This case illustrates the serious influence of sores and ulcers on the metabolism of diabetics and also the persistence and care which must be exercised in restoring the blood sugar to normal.

CONCLUSIONS

1. It is important to distinguish between blood sugar level and the renal threshold for sugar. The height of the blood sugar level at which appreciable quantities of sugar are eliminated in the urine is considered the renal threshold. The blood sugar level in various stages of diabetes may be much higher or lower than this point.

2. There is no striking relation between the height of the renal threshold and the duration of the diabetes. It would appear, however, from the analysis of our sixty-five cases that the threshold tends to rise with the increasing duration of the disease.

3. Younger diabetics as a rule have low or normal thresholds. The threshold rises with advancing years.

4. When the diabetes is mild or quiescent, the point at which the kidneys eliminate sugar is stationary; but when the disease becomes progressive, the threshold tends to rise. Indeed, before death the blood sugar renal threshold may reach great heights with little or no sugar appearing in the urine.

5. A rising renal threshold for sugar in the face of careful dietary treatment is a serious prognostic sign.

6. A high renal threshold for sugar in mild diabetes under proper dietary regulations usually indicates some complication, as arterial hypertension.

7. A high renal threshold for sugar may mean a physiologic expedient to conserve food material.

8. Our experience leads us to the belief that persistent high blood sugar levels promote exhaustion and rapid decline of function, and the high threshold is merely a safety measure.

9. In severe diabetes, where extremely low diets are necessary to maintain life, the high threshold is essential to take care of the seriously impaired carbohydrate metabolism.

10. In the treatment of diabetes it is desirable to maintain the blood sugar level as nearly normal as possible, even though severe restrictions in diet may be necessary for this purpose, notwithstanding the fact that the high threshold will permit of a much more liberal diet without the appearance of sugar in the urine.

11. We regard with misgiving and apprehension any plan of treatment of diabetes which permits of food just short of the point of glycosuria. In short, we believe that diabetes should be controlled on the basis of the blood sugar level rather than by urine tests.

12. A persistent low blood sugar level may be regarded as an extremely favorable prognostic sign.

13. A persistent high blood sugar level, in spite of undernutrition, usually points to an unfavorable outcome.

14. In our experience, cases which hitherto had been intractable and had shown progressive loss of food tolerance, when the blood sugar level was disregarded, have been greatly benefited and their tolerance increased by regulating the food intake so as to insure, when possible, a normal blood sugar level.

15. While we regard 0.15 per cent. as the maximum normal digestion blood sugar level, we believe patients are safer when this level is not higher than 0.13 per cent.

388 Monroe Avenue.

OBSERVATIONS ON TOLERANCE AND RATE OF UTILIZATION OF GLUCOSE IN A SERIES OF INDIVIDUALS EXHIBITING VARIOUS DEGREES OF DIABETES MELLITUS

JOHN R. WILLIAMS, M.D.
WITH THE COLLABORATION OF
ELEANOR M. HUMPHREYS, B.S.
ROCHESTER, N. Y.

Third Paper

Hamman and Janney have both recently reviewed the literature on this phase of the problem; accordingly, we shall only comment on some of the more important investigations. Hopkins[1] points out that in health a moderate rise up to 0.14 or 0.15 per cent. in blood sugar follows the ingestion of 100 gm. of glucose. The curve reaches its peak in from one half to two hours, then quickly subsides. In disturbed carbohydrate metabolism, a normal sugar concentration may be associated with a most pronounced alimentary hyperglycemia. In diabetes, the hyperglycemia is very pronounced; the peak is reached in from one half to three hours and is prolonged.

According to Taylor and Hutton[2] in the majority of healthy males there is no limit to the assimilation of glucose. Glycosuria does not follow the largest possible ingestion of glucose.

Wilder and Sansum[3] in an elaborate study of the subject raise serious objection to the oral method of glucose administration on the ground that it introduces the questionable factor of absorption. In their studies they made use of the method of continuous intravenous injection at accurately controlled rates devised by Woodyatt, Sansum, and Wilder.[4] They conclude that when sugar appears in the urine, as evidenced by a reduction in Haines' solution, the limit of tolerance is reached. Glycosuria is produced in normals when the rate of injection lies between 0.8 and 0.9 gm. of glucose per kilogram of body weight per hour. Nondiabetic pancreatic disease may evince a lowered tolerance even when alimentary tests show no change.

On the basis of our own experience, the fundamental objection to the work of these investigators is that they do not give weight to the blood sugar levels, which is of primary importance in diabetes.

1. Hopkins, A. H.: Am. J. M. Sc. **149**:254, 1915.
2. Taylor, A. E., and Hutton, F.: J. Biol. Chem. **25**:173, 1916.
3. Wilder, R. M., and Sansum, W. D.: Arch. Int. Med. **19**:311, 1917.
4. Woodyatt, R. T., Sansum, W. D., and Wilder, R. M.: J. A. M. A. **65**:2067, 1915.

Nor do they establish the blood sugar threshold of the kidneys, but merely the rate of injection and amount of glucose which can be introduced into the body up to the point of glycosuria. Janney and Isaacson[5] have made similar objection.

In our studies we used the method suggested by Hamman and Hirschman,[6] with whose conclusions our investigations are in substantial agreement. Janney and Isaacson have recently published an account of the blood sugar test used at the Montefiore Home and Hospital, New York City. In their method, in the administration of the glucose and water, they take into consideration the weight of the individual: 1.75 gm. of sugar are given for each kilogram of body weight. For each gram of glucose, 2.5 c.c. of water are used. We think this procedure an advantage and shall incorporate it in our future study, although it will be seen from an examination of our curves that the relation of the amount of sugar to the weight of the patient is not so important as to vitiate investigations made in the manner suggested by Hamman and Hirschman.[6]

It is the practice of many investigators in this field to make hourly observations on the blood sugar level. We prefer the half-hourly interval proposed by Hamman and Hirschman[6] for the reason that in seven out of eleven nondiabetics the maximum blood sugar level was reached one half hour after the ingestion of the glucose, and at the end of one hour the level in these cases had subsided appreciably.

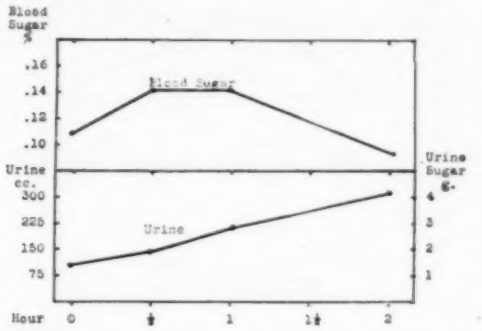
The method as used by us was as follows: Samples of blood and urine are obtained from the fasting patient in the morning. Immediately after, he is given orally 100 gm. of glucose dissolved in water, to which is added the juice of one orange. This is then shaken up with cracked ice and made up to approximately 300 c.c. of fluid; 200 c.c. of water are administered one half and one hour later, at which points further blood and urine specimens are secured, additional and final specimens being secured two hours from the beginning of the test.

GLUCOSE UTILIZATION TESTS IN A GROUP OF NONDIABETICS

The following patients from time to time have passed urine containing a reducing substance which has been thought to be sugar. Some of them have undergone treatment for diabetes. The glucose utilization test employed by us is the one suggested by Hamman and Hirschman.[6] The data are plotted in the accompanying curves. Urine sugar is shown in vertical hatching. Urine volume and blood sugar are plainly indicated in the diagrams. A note of explanation and interpretation follows each curve.

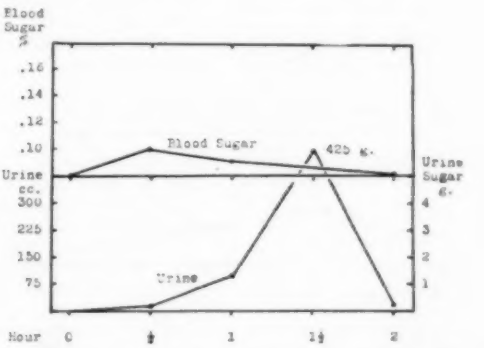
5. Janney, N. W., and Isaacson, V. I.: J. A. M. A. **70**:1131, 1918.
6. Hamman, L., and Hirschman, I.: Arch. Int. Med. **20**:761, 1917.

Chart 1.—Case 1620. Glucose utilization test in a nondiabetic woman aged 34. Body weight, 117 pounds. Hyperthyroidism.



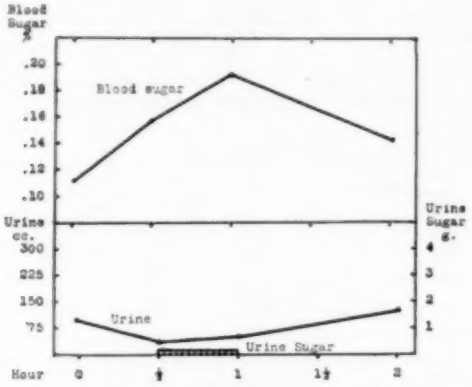
COMMENT.—Attention is called to the slight but appreciable rise in blood sugar in the first half hour. This curve indicates a normal utilization. There was no urine sugar.

Chart 2.—Case 2354. Glucose utilization test in a nondiabetic woman aged 31. Body weight, 114 pounds.



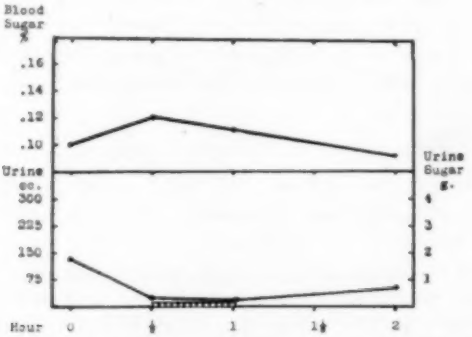
COMMENT.—Sugar is alleged to have been found in the urine of this patient by an irregular practitioner. There is a history of frequent and copious urination; also serious mouth infection. Eleven teeth are crowned and practically all show apical abscesses. There is a slight involvement of the thyroid. The blood sugar curve is below normal.

Chart 3.—Case 2205. Glucose utilization test in a man aged 24. Epilepsy. Body weight, 125 pounds.



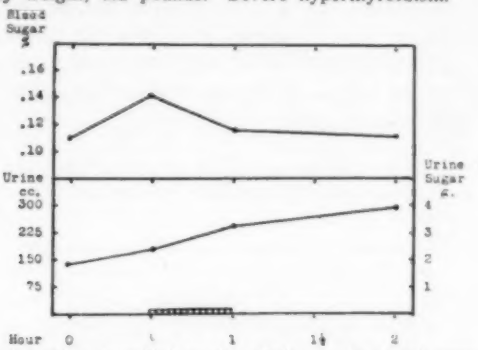
Comment.—The patient has been a victim of epilepsy since 7 months old. His normal blood sugar is approximately 0.11 per cent. (average of four tests). The utilization test was made, then the patient was given 3 grains of anterior pituitary gland daily for three days and the glucose utilization test repeated. The results of each test were strikingly similar. This curve, which is higher than normal, suggests some disturbance in metabolism which may be general in character. The blood uric acid was 5 mg. per 100 c.c., urea 50 mg. per 100 c.c. (average of two tests), cholesterol 187 mg. per 100 c.c.; general nutrition poor.

Chart 4.—Case 2208. Glucose utilization test in a nondiabetic man, aged 54. Body weight, 118 pounds. Mild chronic diffuse nephritis.



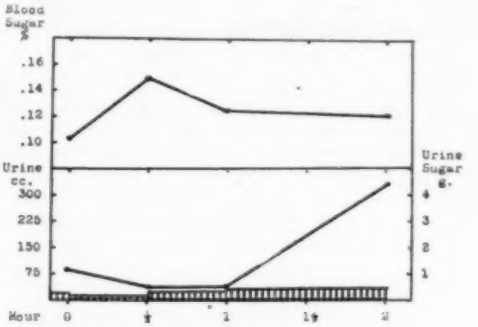
Comment.—When this patient was admitted to the hospital one month previous to this examination and while on a moderately restricted carbohydrate diet, three blood sugar determinations were as follows: 0.17, 0.14, 0.15 per cent. Several blood ureas with patient on a low protein diet ranged from 50 to 89 mg. per 100 c.c. blood.

Chart 5.—Case 2224. Glucose utilization test in a nondiabetic woman aged 22. Body weight, 102 pounds. Severe hyperthyroidism.



COMMENT.—Attention is called to the slight rise in blood sugar in the first half hour. A trace of sugar appeared in the hour urine sample. This curve is essentially normal.

Chart 6.—Case 1352. Glucose utilization test in a nondiabetic man aged 23. Body weight, 150 pounds.



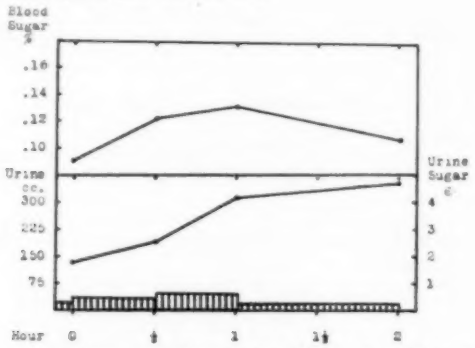
COMMENT.—This patient was rejected for life insurance because sugar was alleged to have been found in the urine. A reducing substance was found in the urine which was levorotatory. Its identity was not clearly established because of lack of necessary reagents. Obviously it was not glucose. The graph shows that it was present in the urine in small amounts with the blood sugar 0.10 per cent. and that the blood sugar curve was not abnormally influenced by the oral administration of the 100 gm. of glucose.

GLUCOSE UTILIZATION TESTS IN A SERIES OF SUPPOSED DIABETICS

We have studied, after the plan of Hamman and Hirschman,[6] five patients in whom there has been a history of probable glycosuria. All of these patients have from time to time been treated for diabetes mellitus for the reason that copper reducing substances have been found in the urine. None gives a typical blood sugar curve observed in true diabetes; in fact, the curves do not differ from those observed in normals. In Cases 2232 and 2394, the figures given as urinary sugar are based on reduction tests using Benedict's quantitative solu-

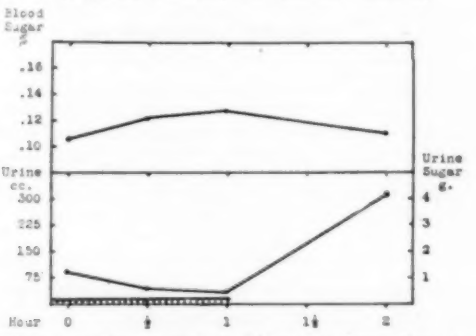
tion. We later studied the reducing substance passed by these two patients and established that it is not glucose but probably some conjugate of glycuronic acid. Inability to secure the necessary reagents prevents the definite recognition of these substances. Some cases of the character shown in this group are undoubtedly renal diabetes, of which Case 2228 is an example.

Chart 7.—Case 2228. Glucose utilization test in a man aged 44. Probably renal diabetes. Body weight, 132 pounds.



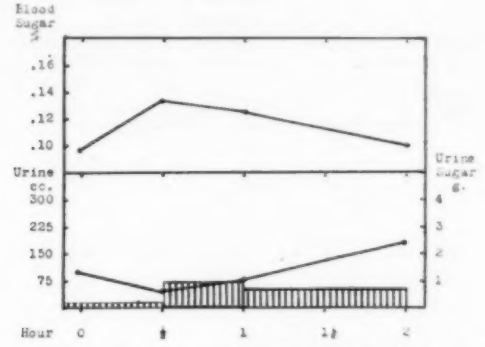
COMMENT.—This patient complains only of loss of weight. Small amounts of sugar have been found in the urine with the patient on a general diet. At the beginning of the test a trace of sugar was found in the urine, with blood sugar at 0.09 per cent., indicating a low threshold. The blood sugar curve is normal, indicating satisfactory utilization of glucose.

Chart 8.—Case 2232. Glucose utilization test in a boy aged 14. Body weight, 94 pounds. Supposed diabetic, but probably normal.



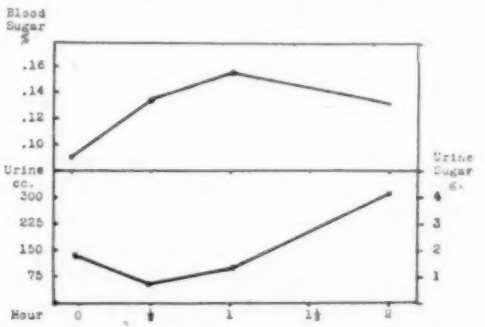
COMMENT.—This boy has passed in his urine from time to time for the past three years copper reducing substances. This has led to the assumption that he has diabetes; accordingly he has undergone sporadic dietary treatment. The copper reducing substance in the urine is levorotatory, does not form the characteristic crystals with phenylhydrazin, and is probably a conjugate of glycuronic acid. The utilization of glucose in this case is normal. The test was of distinct value in determining whether or not the patient had a failure of carbohydrate metabolism.

Chart 9.—Case 2394. Glucose utilization test in a man aged 67. Probable renal diabetes. Body weight, 143 pounds.



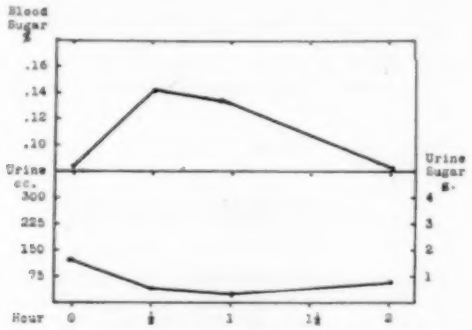
COMMENT.—This patient has passed copper reducing substances in urine for five years, during which time he has been subjected to diabetic dietary and other treatment. Even on a general diet, the reducing substance is never present except in small amounts, is levorotatory, and does not form characteristic glucosazone crystals with phenylhydrazin. Digestion blood sugar ranges normally from 0.09 to 0.13 per cent. The usual clinical symptoms of diabetes have been absent. During the above utilization test the patient did pass appreciable amounts of glucose with blood sugar levels below 0.10 per cent.; accordingly this case might be interpreted as one showing at times the phenomena of renal diabetes.

Chart 10.—Case 2283. Glucose utilization test in a nondiabetic woman aged 20. Body weight, 122 pounds.



COMMENT.—A reducing substance thought to have been sugar was first found in this patient's urine in 1912. Since then the patient has had sporadic dietary treatment for diabetes. There is a history of epigastric distress, tenderness over the gallbladder, belching of gas, etc., suggesting a mild cholecystitis with possible pancreatic involvement. In our experience, such cases frequently show a slight glycosuria. The curves in chart 10 are practically normal.

Chart 11.—Case 2303. Glucose utilization test in a nondiabetic man aged 37. Body weight, 162 pounds.

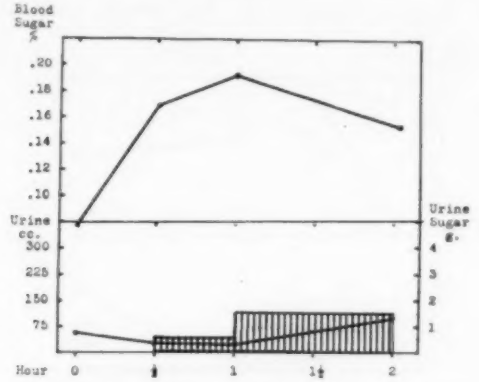


COMMENT.—A copper reducing substance has been found in this patient's urine on several occasions by his family physician. There is nothing in his clinical history to suggest diabetes. It is quite evident that he is able to utilize the large amount of glucose in this test in a normal manner.

GLUCOSE UTILIZATION TESTS IN A GROUP OF VERY MILD OR DOUBTFUL DIABETICS

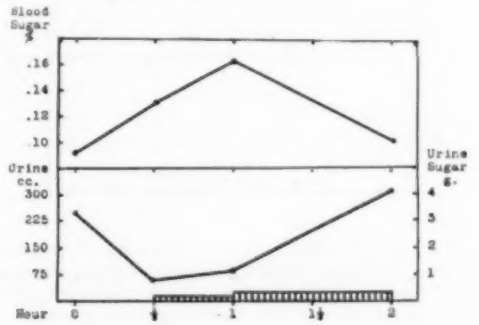
The following patients have shown from time to time traces of reducing substance in the urine. The absence of symptoms and the variability of the findings have given rise to doubt in the minds of many of the physicians who have examined these patients as to whether or not they have true diabetes. The rather high blood sugar within the half hour after the ingestion of the sugar, together with its persistence for an hour or so, the appearance of increased urine sugar, and the diuresis, all, in a very mild degree, point to the early stage of diabetes.

Chart 12.—Case 1594. Glucose utilization test in a man aged 41. Very mild diabetes. Body weight, 150 pounds.



COMMENT.—There is a complete absence of diabetic symptoms in this case. Sugar was first discovered in the urine in the course of a casual examination, and since has been found only occasionally although the patient lives on a very liberal diet. The prompt rise in the blood sugar curve, its persistence at a higher level than normal, together with the glycosuria, suggest a mild diabetes.

Chart 13.—Case 1716. Glucose utilization test in a man aged 47. Very mild diabetes. Body weight, 200 pounds.



COMMENT.—In this case also there is a complete absence of symptoms of diabetes. The patient lives on an unrestricted diet, with only an occasional trace of sugar in the urine. The curves suggest a very mild, indeed, a doubtful, diabetes.

Chart 14.—Case 2230. Glucose utilization tests in a man aged 23. Very mild diabetes. Low grade tuberculosis. Body weight, 140 pounds. Curve A.

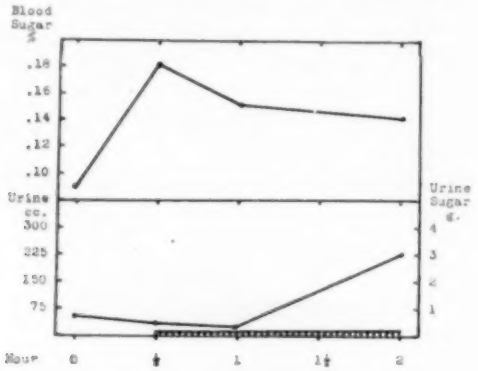
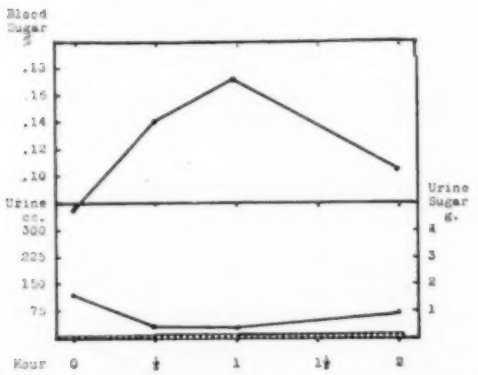
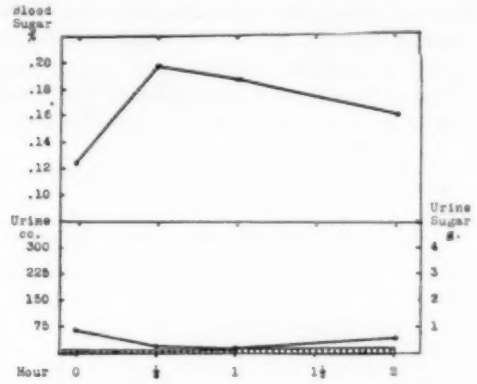


Chart 15.—Case 2230. Curve B.



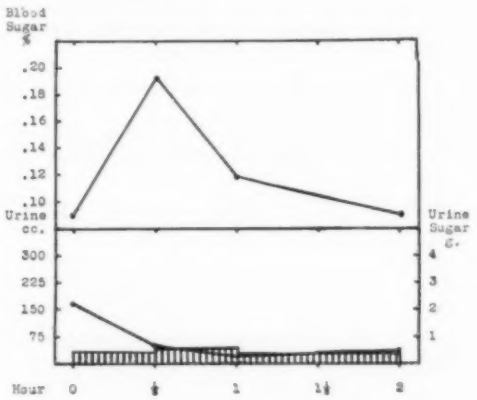
COMMENT.—This patient exhibits none of the clinical symptoms of diabetes. Sugar was found in the urine in the course of a routine examination in the Monroe County Tuberculosis Sanatorium. The examination shown in curve B was made approximately five months later than that shown in A. They coincide fairly well and suggest, as do the other curves in this group, a very mild diabetes.

Chart 16.—Case 2217. Glucose utilization test in a woman aged 56. Cardiac hypertension. Mild diabetes. Body weight, 135 pounds.



COMMENT.—This patient exhibits none of the clinical symptoms of diabetes. Traces of sugar are frequently found in the urine. The blood sugar curve in this test, as in the preceding cases, points to a very mild diabetes.

Chart 17.—Case 1948. Glucose utilization test in a man aged 38. Very mild diabetes. Body weight, 148 pounds.

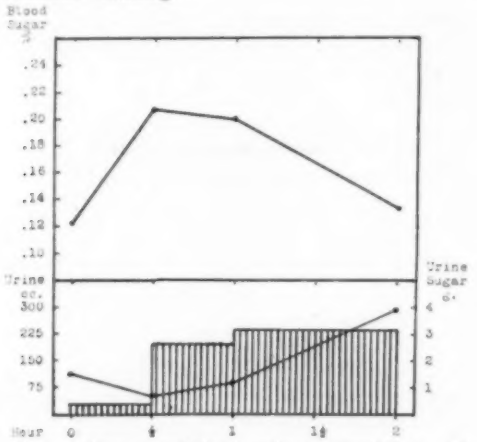


COMMENT.—This patient complained only of loss of weight. Even on the most generous diets this patient shows sugar in the urine only occasionally. His digestion blood sugar level is usually about 0.11 per cent., and has never been found higher than 0.14 per cent. The sharp rise of the blood sugar curve in this test with the glycosuria suggests a slightly diminished carbohydrate metabolism.

GLUCOSE UTILIZATION TESTS IN A SERIES OF CASES OF MILD BUT DEFINITE DIABETES

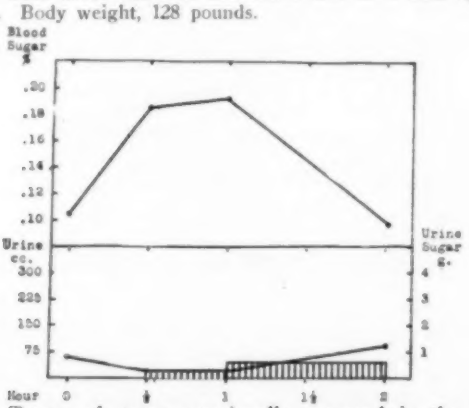
In the following group are those patients who showed definite clinical symptoms of diabetes, as loss of weight, polyuria, thirst, etc. They are very mild in character, however, and very amenable to treatment. This group is typical of a large number of patients who pay no attention to their diabetes and suffer very little from its discomforts.

Chart 18.—Case 2404. Glucose utilization test in a man aged 34. Mild diabetes of five months' standing.



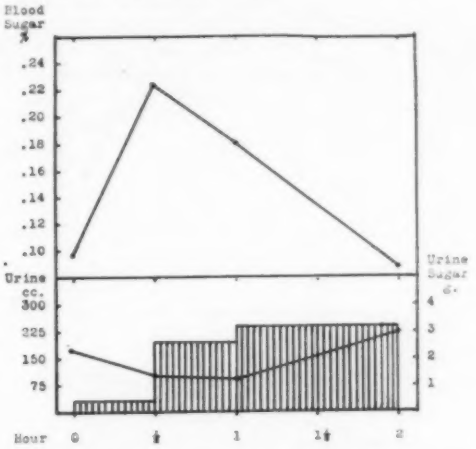
Comment.—This patient complained only of weakness. Sugar found in the urine in small amounts frequently but not constantly. The blood sugar curve shows an undoubted failure in sugar metabolism.

Chart 19.—Case 1000. Glucose utilization test in a man aged 26. Very mild diabetes. Body weight, 128 pounds.



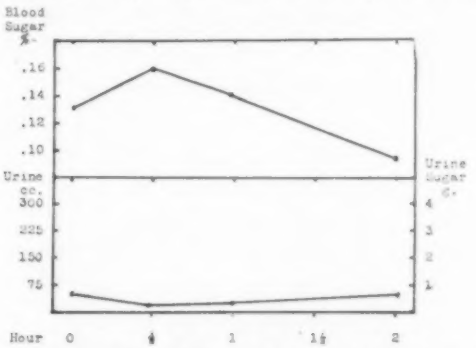
Comment.—Traces of sugar occasionally appeared in the urine of this patient at irregular intervals and while on a general diet. The blood sugar curve dropped to normal at the end of two hours, suggesting but little impairment in the power of utilization.

Chart 20.—Case 2435. Glucose utilization test in a man aged 34. Very mild diabetes. Body weight, 114 pounds.



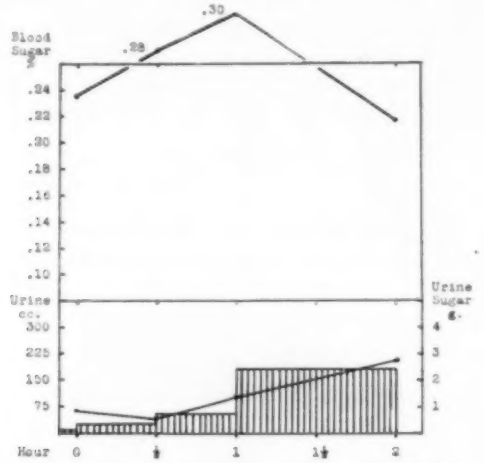
Comment.—This patient gave a history of considerable loss of weight and weakness extending over a period of four years. There was an absence of thirst and polyuria. Sugar was present in his urine only occasionally even on a heavy diet. The low initial blood sugar and the prompt return to normal two hours after the ingestion of the sugar point to the slight failure in ability of the body to utilize glucose, while the sharp rise in the curve together with the glycosuria are evidences of abnormal metabolism.

Chart 21.—Case 2140. Glucose utilization test in a man aged 38. Diabetes of one year's standing. Body weight, 210 pounds. Apparent recovery.



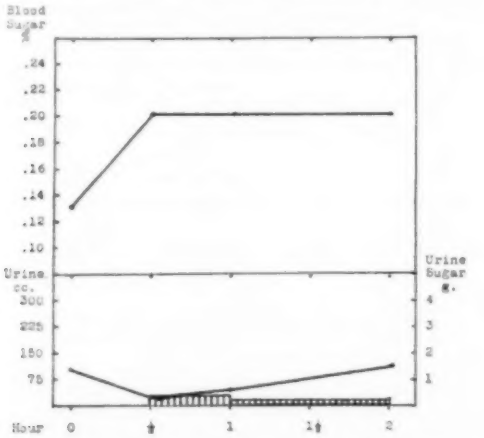
Comment.—Patient is a physician. One year before, on a moderately restricted diet, patient excreted urine of a specific gravity 1.045; urine sugar 3.8 per cent., blood sugar 0.25 per cent. Several subsequent examinations of blood sugar were from 0.20 down to 0.11 per cent. during the course of treatment. For several months patient has been following a general diet, with no restrictions except as to amount of cane sugar, which is eaten sparingly. This test suggests a normal utilization of glucose.

Chart 22.—Case 2348. Glucose utilization test in a man aged 35. Mild diabetes of three months' standing. Body weight, 186 pounds.



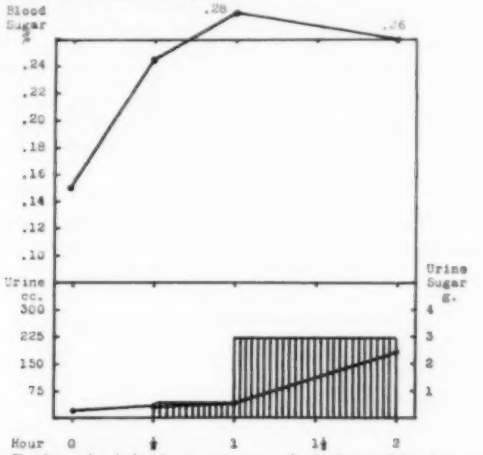
Comment.—This patient exhibited very slight but definite clinical evidence of diabetes. This is shown unmistakably in the blood sugar curve. He yielded promptly to treatment and was able to return to a diet which, aside from its cane sugar content, was fairly normal.

Chart 23.—Case 2324. Glucose utilization test in a man aged 61. Mild diabetes of four years' standing. Body weight, 173 pounds.



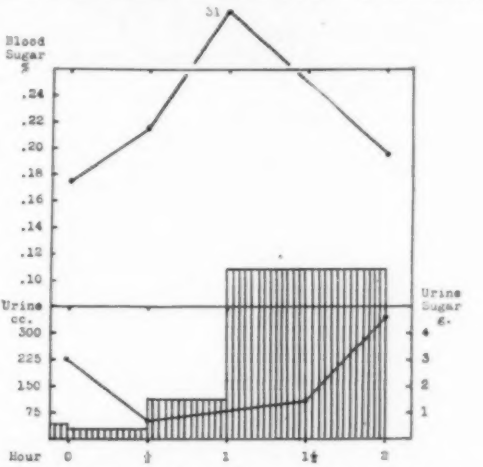
Comment.—There was an absence of the usual clinical symptoms of diabetes in this case, pointing to the mildness of the disease. The blood sugar curve shows a pronounced rise and maintains a persistently high level, which, with the glycosuria, points to defective glucose utilization.

Chart 24.—Case 2476. Glucose utilization test in a man aged 70. Mild diabetes of two years' standing associated with chronic cholecystitis and pancreatitis. Body weight, 130 pounds.



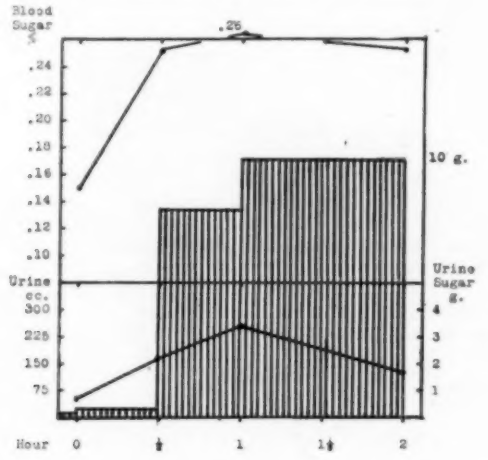
COMMENT.—Patient had had symptoms of cholecystitis for more than ten years. He has had none of the clinical symptoms of diabetes except that on a generous diet he excretes small amounts of sugar in the urine. In the experience of the writers, the diabetes associated with cholecystitis is usually of the mild character exhibited by this patient.

Chart 25.—Case 2338. Glucose utilization test in a man aged 61. Mild diabetes of about three months' standing. Body weight, 200 pounds.



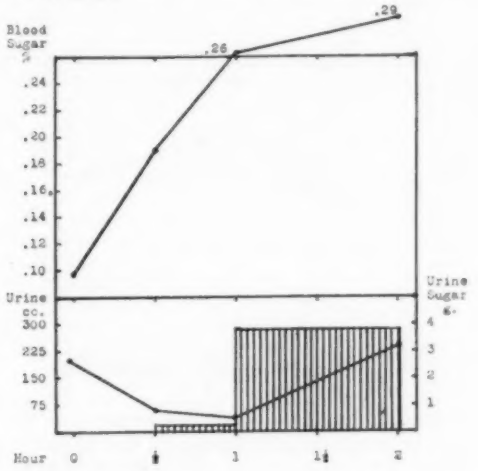
COMMENT.—This patient exhibited but very slight clinical evidence of diabetes in a gradual loss of weight. On a liberal diet in which cane sugar is eliminated and foods containing high percentages of starch are limited, he maintains a digestion blood sugar level of from 0.09 to 0.14 per cent. He must, therefore, be classed as a mild diabetic. The graph in this case shows a definite failure in sugar utilization.

Chart 26.—Case 2289. Glucose utilization test in a woman aged 58. Mild diabetes of five months' standing. Body weight, 150 pounds.



Comment.—This patient had none of the clinical symptoms of diabetes except a slight eczema of the vulva. Her urine, even on a very liberal diet, showed small amounts of sugar inconstantly. Her digestion blood sugar level on slightly restricted diets ranges from 0.09 to 0.15 per cent.; hence it will be seen that she has a mild diabetes. The graph of the utilization test, however, points clearly to a definite failure in carbohydrate metabolism.

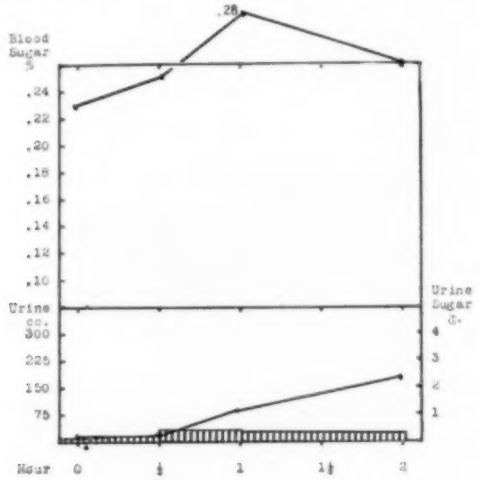
Chart 27.—Case 2309. Glucose utilization test in a woman aged 51. Mild diabetes and cardiac hypertension. Illness dates over a period of four years. Body weight, 148 pounds.



COMMENT.—There were no clinical symptoms of diabetes in this case; all of the evidence of illness present seemed related to the rather serious high arterial pressure. The patient's blood sugar on a rather liberal diabetic diet, 120 gm. of carbohydrate, 1,900 calories, ranged from 0.10 to 0.12 per cent. It is possible that this patient has not diabetes but that the striking rise and persistence of the high blood sugar curve, together with the well marked glycosuria, is due to the same cause. The blood urea in this case was slightly above normal, ranging from 40 to 46 mg. per 100 c.c. blood, and a two-hour renal study after the method of Mosenthal[7] showed little evidence of renal involvement. This graph was puzzling to the writers. The test was therefore repeated after an interval of two weeks, with practically the same result. On each occasion the blood sugar on the day following the test returned to a level of approximately 0.11 per cent. It is probable that this case represents a very mild diabetes associated with arterial hypertension of endocrinal origin.

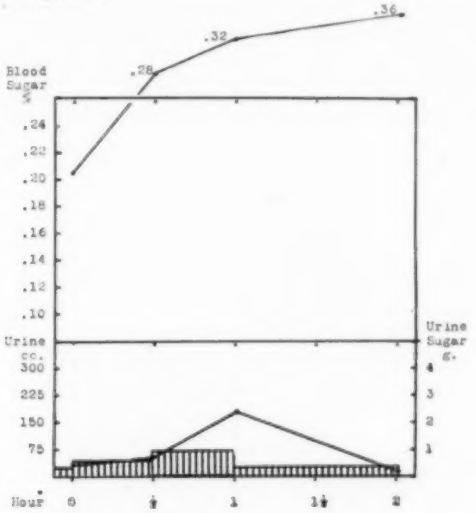
7. Mosenthal, H. O.: Arch. Int. Med. **16**:733, 1915.

Chart 28.—Case 2440. Glucose utilization test in a woman aged 54. Mild diabetes; cardiac hypertension associated with endocrinal disturbance. Body weight, 165 pounds.



COMMENT.—This patient had a high blood sugar renal threshold—about 0.22 per cent. Her blood sugar level was affected appreciably by emotional influences as is shown elsewhere. This graph, together with the data afforded by other blood sugar estimations, leads to the conclusion that she has a mild diabetes.

Chart 29.—Case 2442. Glucose utilization test in a woman aged 65. Mild diabetes of recent origin in association with severe arterial hypertension. Body weight, 114 pounds.

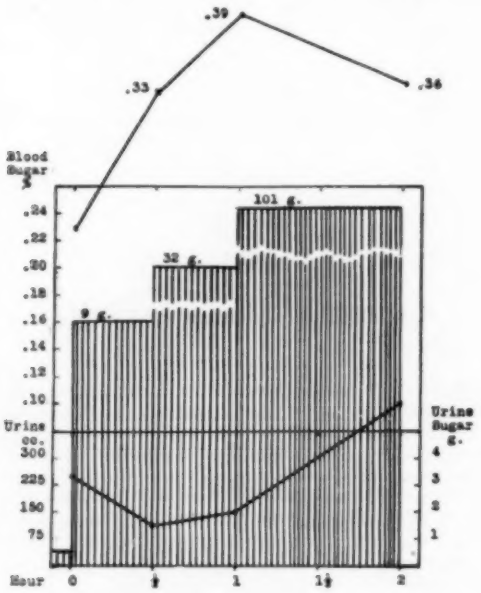


COMMENT.—Before the test represented in chart 29 was made, for seven days the patient had been on a diet containing approximately 180 gm. of carbohydrate and totaling about 2,000 calories. On this diet the blood sugar level ranged from 0.10 to 0.12 per cent. and she passed daily from 4 to 11 gm. of sugar in the urine. This would suggest an unusually low threshold. Five days after the test on the same diet, the patient was urine-sugar-free and her blood sugar level was 0.19 per cent., a rather high threshold. Urea studies and a Mosenthal[7] two-hour renal investigation indicate normally functioning kidneys. It seems quite probable, therefore, that there is some extrarenal factor influencing the blood sugar level in this case.

GLUCOSE UTILIZATION TESTS IN A SERIES OF CASES OF MODERATELY SEVERE DIABETES

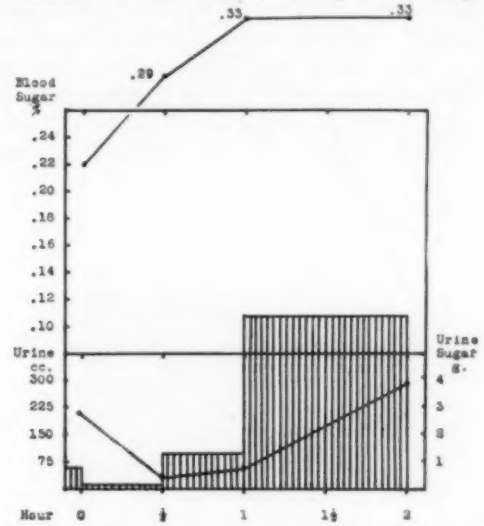
The following group of cases show more pronounced clinical evidence of diabetes, yet with the single exception of Case 2329, which has since terminated fatally, none of the patients can be classed as being more than moderately ill.

Chart 30.—Case 2279. Glucose utilization test in a woman aged 43. Moderately severe diabetes of one month's standing. Body weight, 128 pounds.



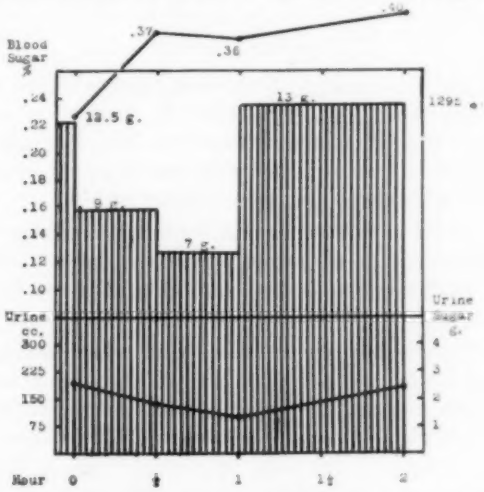
Comment.—The interesting feature of this case is the high renal threshold exhibited. On three occasions preceding the foregoing test, and at intervals of five days, blood sugar determinations were made and were, respectively, 0.20, 0.13, and 0.22 per cent. On each occasion the patient was urine-sugar-free so that the threshold must lie above 0.22 per cent., or, as shown in this graph, at 0.23 per cent.

Chart 31.—Case 1001. Glucose utilization test in a woman aged 56. Moderately severe diabetes of four months' standing. Body weight, 180 pounds.



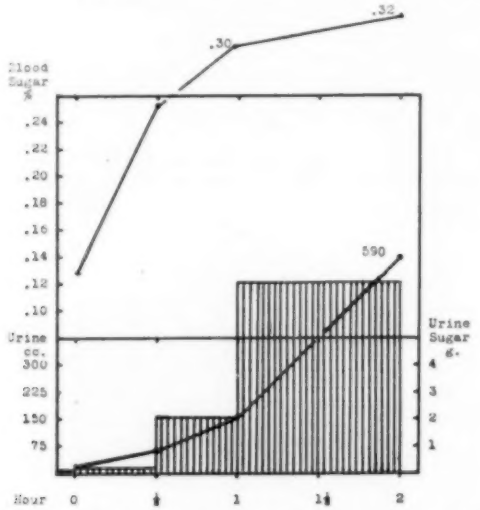
Comment.—This patient, like the preceding one, had a high renal blood sugar threshold and a high blood sugar level. The noteworthy failure of sugar utilization is evident in these cases.

Chart 32.—Case 2399. Glucose utilization test in a man aged 54. Moderately severe diabetes of one month's standing. Body weight, 134 pounds.



Comment.—This case represents the early stage of an acute moderately severe diabetes which yielded promptly to treatment. The graph shows strikingly the comparative degree of metabolic failure.

Chart 33.—Case 2329. Glucose utilization test in a woman aged 32. Severe diabetes of less than one month's standing. Body weight, 103 pounds.



COMMENT.—This patient had all of the clinical symptoms of rather severe diabetes, including thirst, polyuria, and loss of weight. In many respects she was quite a remarkable case. Throughout the period of observation of forty days she showed a rather low blood sugar and a severe acidosis, even when on a practically fat-free diet. The data of this interesting case are plotted elsewhere. It terminated fatally one month after the last observation.

CONCLUSIONS

1. The glucose tolerance and utilization test proposed by Hamman and Hirschman[6] and as later modified by Janney[5] is an extremely useful procedure in differentiating those but little understood metabolic disorders in which traces of reducing substance are excreted in the urine from renal diabetes and mild diabetes mellitus.

2. As a means of measuring the degree of disturbance in carbohydrate metabolism in hyperthyroidism and other endocrinal disorders, it is much superior to tests depending solely on the determination of urine sugar.

3. Many persons are rejected for life insurance and are treated as diabetics because of the occasional or even frequent finding in the urine of copper reducing substance. Tests on a series of these cases indicating a normal power to utilize glucose are here shown.

4. Renal diabetes is a definite physiologic disturbance, easily distinguishable by this procedure from true diabetes.

5. The sugar tolerance and utilization test is particularly useful in differentiating those cases of very mild diabetes in which there are exhibited no clinical symptoms of the disorder. The various degrees of failure of carbohydrate metabolism in the more evident cases of diabetes are most strikingly shown by this method.

THE EPIDEMIC OF INFLUENZA AT CAMP MERRITT, N. J.

FRANCIS M. RACKEMANN, M.D. (Boston)
First Lieutenant, M. C., U. S. Army

AND

SAMUEL BROCK, M.D. (New York)
First Lieutenant, M. C., U. S. Army

CAMP MERRITT, N. J.

During the recent pandemic of influenza, September to November, 1918, several observations as to the nature and general character of the disease and of the epidemic have been made at U. S. A. Base Hospital, Camp Merritt, N. J. It is the purpose of the present work to present some of these observations with respect to: (*a*) the clinical and pathologic picture of influenza and bronchopneumonia; (*b*) the importance of secondary invaders in the latter part of the epidemic, and (*c*) the change in character of the latter part of the epidemic consequent on the activity of these secondary invaders.

In all the literature on this epidemic, both lay and scientific, certain distinctions have been made between influenza as such, and a concomitant or complicating bronchopneumonia. It has seemed to us more rational to regard this so-called "bronchopneumonia" not so much a complication as a severe manifestation of the disease itself. Christian[1] has recently discussed this same point. It is, however, convenient to employ the word "influenza" for the early stage and the word "bronchopneumonia" for the later stage of the disease.

From Sept. 19 to Nov. 6, 1918, 4,979 cases of influenza were treated at this hospital. Of these 4,979 cases, 1,015, or 20.4 per cent., developed bronchopneumonia, and of these latter, 31 per cent. died — a mortality for all the admissions of 6.3 per cent. It is unnecessary to say that all deaths were in this late or serious group and that the development of chest signs and symptoms enabled the diagnosis of bronchopneumonia to be made in each and every fatal case. Chart 1 shows the progress of the epidemic from day to day.

It is seen from Chart 1 that the incidence of new cases of influenza reached its height in about ten days after the start of the epidemic; that new cases of bronchopneumonia reached their maximum three days later; and that the summit of the death curve came nine days after

1. Christian, H. A.: Incorrectness of the Diagnosis of Death from Influenza, J. A. M. A. **71**:1565, 1918.

the influenza maximum. These various heights correspond accurately to the average period of onset and the average duration of total fever, as will be discussed below.

From the chart it would appear that the daily death rate was increasing throughout the epidemic, but we hope to demonstrate later that the character of the disease changed very remarkably, resulting in a clinical course which was often prolonged, so that in these cases death was delayed.

Before considering the epidemic as a whole we will discuss the course of the disease through its various stages.

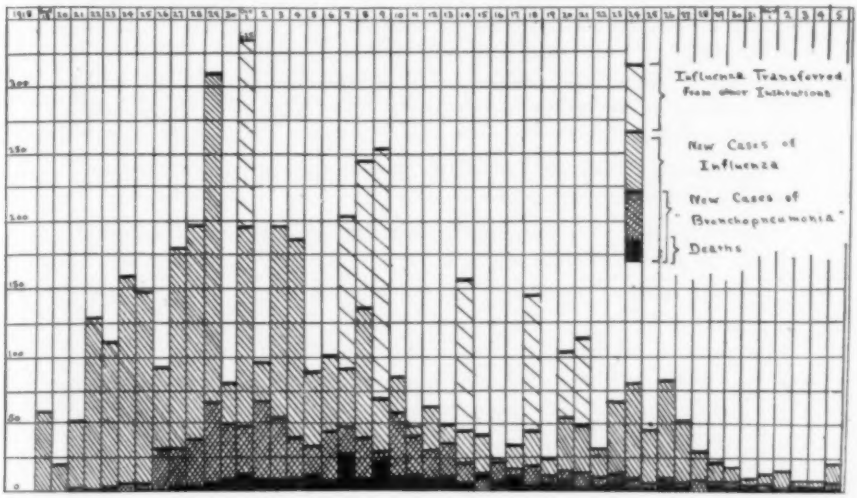


Chart 1.—Daily incidence.

UNCOMPLICATED INFLUENZA

Clinical Picture.—The clinical picture of this disease in the early stages was very striking. Each case seemed exactly like its fellow, so that at first the patients in each individual ward presented a very homogeneous picture. The symptomalogy has been so well described by Keegan[2] that further discussion here is unnecessary except to emphasize the more important points on which the diagnosis was made: the extreme and characteristic prostration; the history of very sudden onset — from health to prostration without warning often in a few hours; the general complaint of headache, with generalized muscular pains through the trunk and limbs; the high fever and the essentially negative physical examination.

2. Keegan, J. J.: The Prevailing Epidemic of Influenza, J. A. M. A. **71**:1051, 1918.

A few of the early typical cases (perhaps 10 or 15 per cent.) presented a very faint pinkish macular eruption on the face, neck and anterior chest which often simulated the early eruption of measles, but which usually cleared up in about eighteen hours. The pharynx was usually red, at times showing small punctate hemorrhagic spots, but no enanthem or true Koplik spots were ever seen. Epistaxis was frequent, often severe. The lungs showed in a small proportion of cases a few râles at the bases, but this was by no means a characteristic finding.

The clinical course was rapid. In the majority of these cases, the temperature fell to normal, usually subnormal, within four days, leaving the patient still prostrated and weak. The pulse was not rapid; at the height of the disease it was full and showed a tendency to dicrotism. Immediately after the fall in temperature the bradycardia was striking; observations of as low as fifty beats per minute being not infrequent.

Laboratory Findings.—In these early influenza cases, laboratory findings were disappointing.

Blood cultures on hormone gelatin broth[3] (10 c.c. of blood in 100 c.c. of medium) were sterile in each of the nine cases studied.

Throat cultures planted on Loeffler's blood serum gave a mixture of organisms in each of thirty cases. Similar throat cultures from the same patients streaked on defibrinated blood infusion agar plates showed nonhemolytic streptococci in seventeen cases, in two of which they were associated with pneumococci, and in three others with gram-negative influenza-like bacilli. In four cases gram-positive diplococci predominated, and two showed only staphylococci.

Postnasal cultures were streaked on laked blood hormone agar[3] plates and showed a mixture of organisms in seventeen; a predominance of gram-negative influenza-like bacilli in five; while in two there was no growth.

Total leukocytes were counted on the first day of admission in ten cases, and averaged 9,200 cells per cubic millimeter. On the fourth day, in the same patients, they averaged 8,500, at which time none of these patients had developed pneumonia. A study of the *sputum* was anticipated, but these patients in the early stage of the disease did not raise suitable sputum, in spite of the fact that coughing was often a definite symptom.

Treatment of these early "influenza" cases resolved itself into three objects: First, a vigorous attempt to dilute toxins, and promote elimination by forcing fluids and by providing free catharsis with

3. Huntoon, F. M.: Hormone Medium, J. Infect. Dis. **23**:169, 1918.

castor oil or magnesium sulphate; second, a symptomatic relief of the headache and muscle pain with acetyl salicylic acid combined with alkali or with Dover's powder, and of the cough with expectorants or sedatives (codein) as indicated; and third, the very important and close study of the chest to determine at the earliest moment the development of pathologic physical signs in the lungs, with the view not only of changing the treatment, but, more important, of isolating the patient in a pneumonia ward as soon as possible.

BRONCHOPNEUMONIA

Clinical Picture.—Quite as typical in its clinical unity as influenza proper was the serious manifestation of this infection spoken of as "bronchopneumonia." We wish to describe a set of symptoms and signs with the attending pathologic changes which mark the severe stages of influenza. After the first symptom of influenza, the average time of onset of this manifestation was 4.03 days in a series of 726 recovered cases, and 5.7 days in a series of forty-seven fatal cases.

The diagnosis of bronchopneumonia was made as follows: As was said in the foregoing, the uncomplicated upper respiratory tract influenza was associated with a fall in temperature, pulse and respiration to normal on the second, third, or, more usually, on the fourth day of the disease. In the bronchopneumonia cases, however, the temperature maintained itself or even rose higher at this time, the pulse became rapid, and of still greater significance, the respiratory rate, which had been between 20 and 24, now ascended, reaching anywhere from 28 to 50 per minute; cyanosis became quite noticeable, cough more severe, and physical examination of the lungs revealed a most constant finding, namely, one or more collections of small moist râles, patchy in distribution, usually located at the bases posteriorly. At this stage, dulness to percussion and the characteristic high-pitched bronchial expiration were usually lacking. On the contrary, there was frequently a diminution or even a suppression of breath sounds in the area affected. Experience soon taught us that in the following twenty-four or forty-eight hours signs of consolidation would appear in an area so affected. The heart, pericardium and abdomen proved uniformly negative.

The clinical picture now became characteristic. The patient was severely prostrated and apathetic: cyanosis of lips, cheeks and finger tips, with dyspnea, was impressive, the severe cough produced a glairy mucous sputum containing a small amount of purulent material; it had not the viscid tenacity of the sputum seen in lobar pneumococcus pneumonia. Blood in the sputum was a frequent finding; it ranged from a mere streaking to a considerable amount, and was reddish or

dark reddish in color, and had not the orange rusty tint seen in lobar pneumonia. Occasionally considerable amounts were expectorated, giving evidence of the hemorrhagic extravasation going on in the pulmonary tissues. Epistaxis, often seen in the earlier stages of the disease, now became quite marked, occasionally even alarming. Headache and chest pain require mention: the latter a more or less constant substernal pain apparently due to the intense acute tracheobronchitis, the former a continuation of the pain of the milder stage, and probably due to cerebral congestion.

In from twelve to seventy-two hours as the patient became more acutely ill, the cyanosis deepened and dyspnea became more marked. Symptoms of the profound intoxication now dominated the picture: abdominal distention; urinary retention; sordes on lips and teeth, and dry, parched, heavily coated tongue with foul breath appeared. Symptoms referable to the central nervous system were at times seen, as twitching of the muscles of the fingers, forearms and face. In this connection the delirium which appeared in all of the fatal, and in a good many of the recovery cases deserves mention. It took on the form either of an active, even maniacal occupational delirium, or more usually the low mumbling type described by the old writers as being associated with the asthenic fevers. Nausea and vomiting were occasionally seen. Jaundice was a rare symptom, probably depending on an increase in the viscidity of the bile and therefore obstructive in origin.

The temperature, pulse and respiration curves differed in the fatal and recovery patients. The fatal cases had a short course (Chart 2); in a series of thirty-nine such cases the duration of the pulmonary involvement averaged only 4.7 days. The temperature curve seldom assumed the sustained plateau so common in lobar pneumococcus pneumonia, but was rather of an irregular, remittent type, ranging from 99 to 105 or even to 107 F.

The pulse rate was usually considerably slower in these primary cases than would ordinarily be expected in a lobar pneumonia of similar severity. However, a stepladder rise in the pulse rate was of serious prognostic import, the continuance of this rise for over three days almost invariably indicating a fatal outcome. Irregularity of the pulse was seldom seen.

Of greater value than either the temperature or the pulse was the respiratory rate, which was always raised. Here again a climb in the rate, sometimes precipitous, usually more gradual, presaged death.

The systolic blood pressure was normal in the acute stage of the disease, the diastolic was at times often as low as 55. With the drop in temperature the systolic pressure also declined, the diastolic pres-

sure remaining low. These relatively low pressures were then maintained for several days, during the period of subnormal temperature and slow pulse, when they slowly recovered. No other marked or consistent observations were made on blood pressure, nor were essentially different observations made in the fatal and recovered cases. Readings within twenty-four hours of death were made in several instances at a time when the pulse was very rapid, but no additional

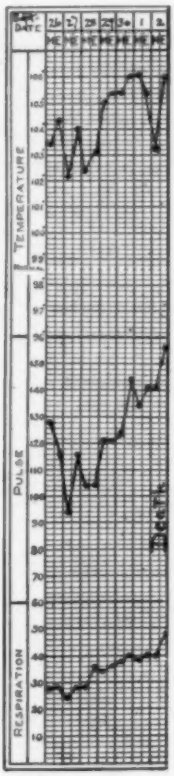


Chart 2.—Temperature, etc., early fatal case.

fall was seen. From these observations we may deduce that in this disease vasomotor tone is depressed, but that the heart's strength remains good to the end.

Total leukocyte counts were made in many cases, but no consistent findings were observed except that in the cases of primary influenzal bronchopneumonia the average count was low (5,000 to 15,000 cells per cubic millimeter). The presence of the hemolytic

streptococcus tended to increase this average count but slightly, although the individual counts varied from 5,000 to 30,000 or even higher. Several cases were observed with counts below 2,000 cells, all of which were fatal.

In a small series of these bronchopneumonia cases the coagulation time of the blood was determined and found normal. The urine showed, as a rule, a trace of albumin with granular and hyaline casts.

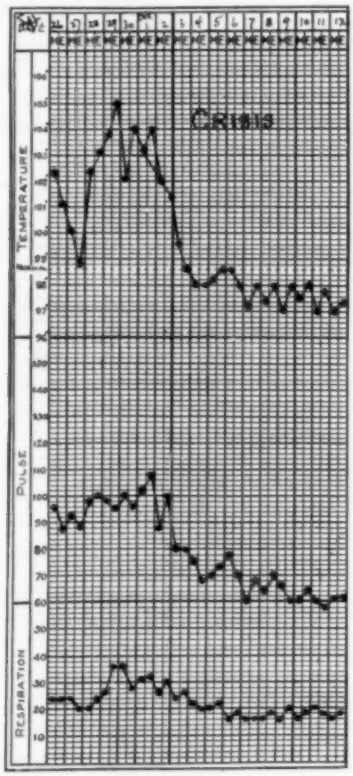


Chart 3.—Temperature, etc., crisis.

Red blood cells were found frequently. No other evidences of renal insufficiency were noted.

In the patients who recovered, the following interesting facts stood forth. In a series of twenty-five such patients, sixteen, or 64 per cent., had a temperature fall by "crisis" (Chart 3); that is, a drop from 102 or 105 to normal in forty-eight hours or less, whereas nine, or 36 per cent., had a defervescence by lysis. In these crisis cases a

decline occurred usually on the third day of the pulmonary involvement; in the lysis cases, usually on the fourth day, in which group an overage of 5.5 days then elapsed before the normal base line was reached.

The pulse and respiratory rate usually dropped in accordance with the temperature, although not infrequently the pulse rate fell to below the normal, reaching 40 or 50 beats per minute for a few days. The respiratory rate occasionally remained considerably elevated for days before it fell to normal. A very interesting corollary to these findings was that, considering the entire disease, by the time the temperature chart had completed its first week's cycle, the patient had either started on his defervescence or else the pulse and respiration had begun their ominous, fatal rise. As a consequence, the black line at the end of the first week on the temperature chart came to be called the "Dead Line."

We have already referred to the physical examination of the lungs at the beginning of bronchopneumonia and emphasized the consonating râles most marked at the lung bases behind. In the more severe cases, moist and dry râles were generalized, being especially marked at the bases and over the interscapular regions. Frequently patients died, some within two days, with no further evidence of pulmonary invasion than these râles. With Christian[1] we have never seen moribund cases without definite chest signs or symptoms. With the advance of the disease, dulness increased, fremitus, bronchovesicular, and finally bronchial breathing were heard most commonly at the bases, especially at the right. A pleuritic friction rub occurred infrequently; signs of pleural effusion were never found. As death approached, the larger moist râles of pulmonary edema dominated the picture.

Bacteriologic findings in these influenzal-bronchopneumonia cases will be discussed later.

Complications and sequelae of this severe infection in a series of 705 cases include:

	No. Cases		No. Cases
1. Otitis media, acute	28	6. Parotitis	7
2. Tonsillitis, acute follicular	15	7. Phlebitis, acute	5
3. Relapse	12	8. Sinusitis, frontal, acute	3
4. Laryngitis, acute	8	9. Emphysema, subcutaneous	3
5. Abscess, subcutaneous	5	10. Epistaxis, very severe	2

Of the seven cases of parotitis, four were clinically simple mumps, while three patients developed such extreme signs of inflammation (heat, redness and swelling) that their parotids were incised. A small amount of pus was evacuated in two cases, one being bilateral. All three patients recovered promptly.

The cases of relapse have been interesting. The diagnosis has been made only in those cases in which the temperature, pulse and respiration not only fell to normal or below 98.6, 70 and 20, respectively, but remained so for at least forty-eight hours. The second attack usually began suddenly in from two to eight days after the normal temperature had been reached. Following a shorter intermission, it

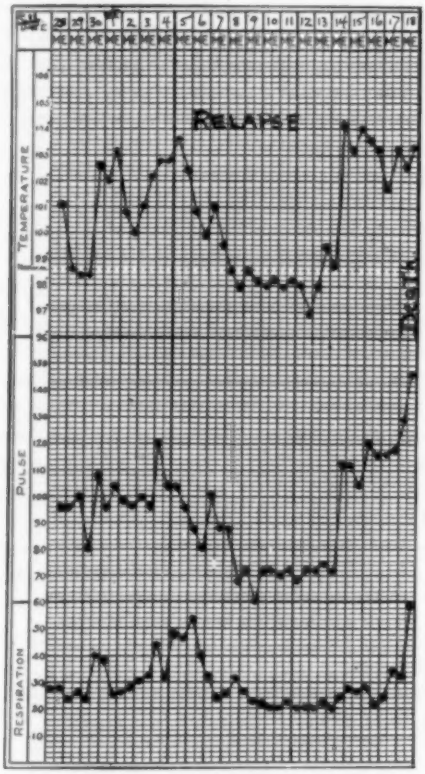


Chart 4.—Temperature, etc., relapse.

was more apt to be severe than after a longer one. On the whole, relapses have been very serious, the patient often dying within four days after the new rise of temperature, with a renewal in aggravated form of all the described symptoms, and usually on physical examination showing new areas of lung involvement. Chart 4 is typical. When the onset of the relapse is delayed, we have noted that in the interval the patient did not exhibit the sense of well-being with

increased appetite, so common in the recovered cases immediately after the fall in temperature.

It is unfortunate that insufficient data are available on the sputum bacteriology of the primary bronchopneumonia and of the relapse to compare them, and thus to decide whether these relapses are true reinfections or are instances of the secondary invasion of lung tissue already weakened. A few cases have shown different organisms in the two attacks.

"Unresolved pneumonias" have been somewhat frequent. Of 635 convalescent patients, 121, or 19 per cent., have shown râles with occasionally slight dulness and harsh breathing over the site of the original lung involvement, persisting for two weeks after the fall in temperature. While no figures are available we believe that practically all of these patients clear up entirely within from four to six weeks after defervescence.

Toward the end of the third week of the epidemic, as seen at this hospital, surprising changes took place. Reports from the laboratory showed an ever-increasing proportion of the hemolytic streptococcus in the sputum. In the early days of the epidemic it was difficult to obtain satisfactory specimens of sputum for study; the cough in the pure "influenza-bronchopneumonia" is usually unproductive of any definite purulent or mucopurulent plugs of sputum, so that washing the sputum was practically impossible, and results could be obtained only by streaking the crude material on blood agar plates.

Chart 5 shows the curves of the daily number of total sputum examinations, as well as the number of each type of organism found. These facts stand forth: the hemolytic streptococcus was at first present in inconsiderable numbers, but in the third and fourth weeks its curve closely approximated the curve of the total examinations. The influenza bacillus at first outnumbered the hemolytic streptococcus, but in the third week, its curve fell below the curve of the latter organism and remained below throughout the epidemic. The pneumococcus curve, in a general way, resembles the influenza curve, not only in their common relationship to the hemolytic streptococcus, but also in that their curves run an essentially parallel course.

Curiously enough, it was recognized that the streptococcus patients seemed to "do better" or at least as well as did the other patients, and further, that the death rate in proportion to the daily admissions seemed to fall markedly. Chart 6 illustrates these facts and demonstrates that, of the patients who entered the ward in the first five-day period, 65 per cent. died, while at the end of the epidemic, none of the patients admitted in the last three five-day periods died. Further-

more, the individual ward was losing its homogeneous appearance. The clinical course of the individual patient was no longer true to the type described.

This sudden and remarkable change in the clinical picture, in laboratory findings, and in necropsies is to be explained by the invasion of secondary organisms and the construction of a new pathology.

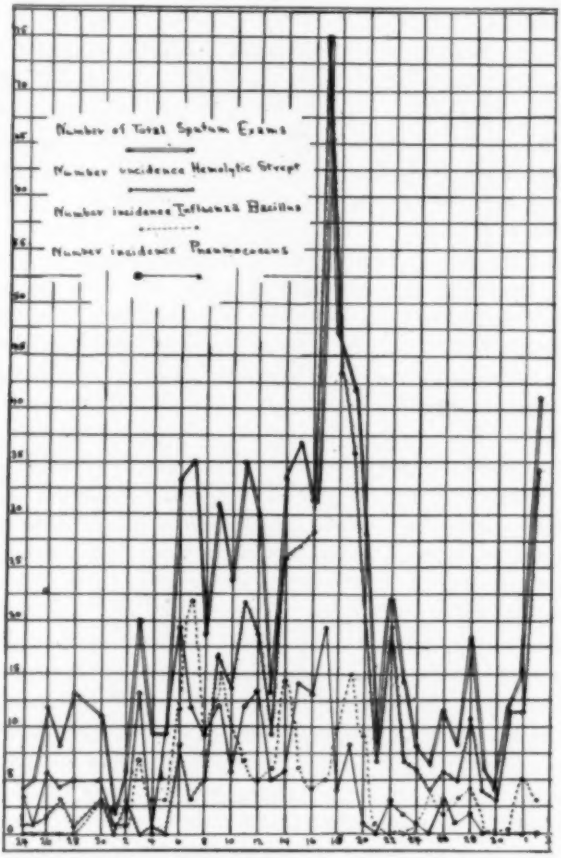

Number of Total Sputum Exams
Number incidence Hemolytic Strept
Number incidence Influenza Bacillus
Number incidence Pneumococcus

Chart 5.—Daily incidence of sputum organisms.

Treatment.—Treatment of the influenzal bronchopneumonias was purely symptomatic, although stress was laid on keeping the intake of total fluids as great as possible. Digitalis, camphor and occasionally strychnin were used in an attempt to control the rising pulse rate; they seemed at times to be effective. When the patient was unable

for any reason to take fluids well and became "dried up," with dry tongue and skin, tap water was given by rectum, and in a few cases salt solution (always made up with freshly distilled water) was injected intravenously in daily doses of 500 c.c. each. On advice that a vaccine containing in 1 c.c., 100 million mixed pneumococci together with 100 million streptococci, 100 million staphylococci, and 100 million influenza bacilli gave good results in these acute cases at U. S. A. General Hospital 1 in New York City, it was tried here on seventeen patients in doses injected intravenously as follows: First day 1 c.c., second day 2 c.c., and third day 3 c.c. The results were very

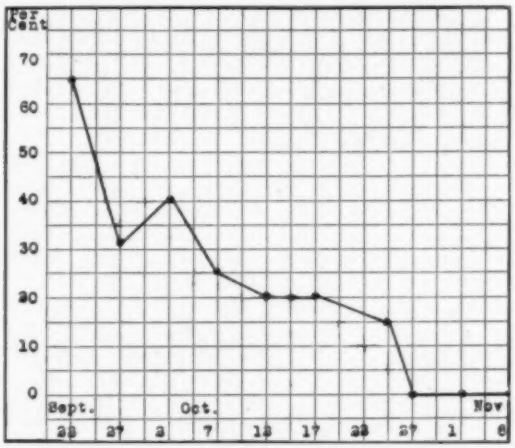


Chart 6.—The variation according to the stage of the epidemic in the average percentage death rate of patients admitted to three typical pneumonia wards during consecutive five-day intervals.

disappointing. Of 17 treated patients, 5 died (29.4 per cent.). Of 26 other patients who entered the ward on the same day as the treated, and therefore served as controls, only 5 died (19.2 per cent.). Furthermore, the total days of fever averaged 11.5 in the treated patients, but only 9.8 in the control series, so that in the vaccinated group the mortality was higher and the duration of illness was longer.

Many of the cases at this time were similar to the now familiar post-measles streptococcus bronchopneumonia described by Cole and MacCallum.[4] The course of the disease became considerably lengthened (Chart 7 is typical); the patients no longer appeared overwhelmed by a virulent toxemia. Beside showing the hemolytic strep-

4. Cole and MacCallum: Pneumonia at a Base Hospital, J. A. M. A. **70**:1146, 1918.

tococcus in such numbers, the sputum became more profuse and purulent.

The most striking change, however, was that whereas in the influenzal type of bronchopneumonia already described, pleural effusions were never encountered, they now became comparatively common complications. Pericarditis was also noted. It is beside our

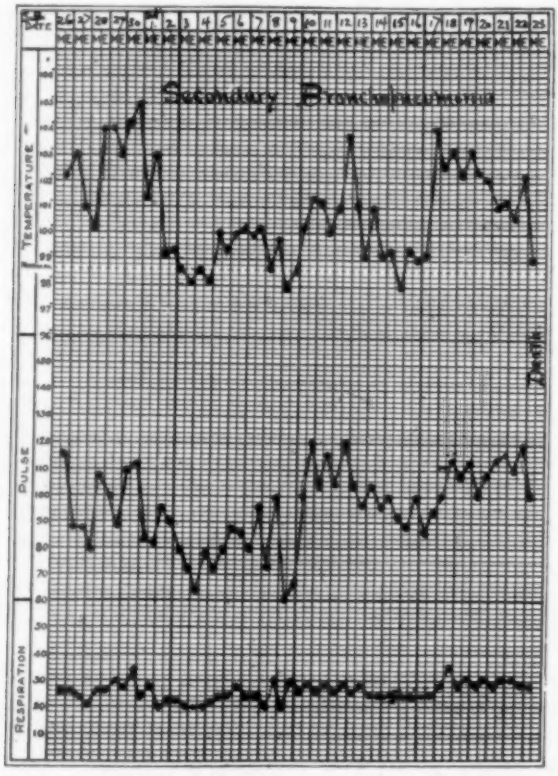


Chart 7.—Temperature, etc. Later case with prolonged course.

purpose to describe this syndrome in further detail, except to speak of our experiences with empyema.

EMPYEMA

By empyema we have reference to the pleuritic effusion complicating bronchopneumonia, regardless of gross appearance or of bacterial flora. The bacteriology of fifty such fluids coming to the laboratory of the hospital from October 1 to November 9 was studied

(Table 1). Brooks and Cecil[5] have studied eighty cases of empyema at Camp Upton, occurring during the months from October, 1917, to and including April, 1918. A considerable number of their empyemas developed in pneumonia following influenza, tonsillitis and other mild infections. The comparison of their results with ours is interesting.

It will be seen in both series, that a little over half the cases were due to the hemolytic streptococcus. On the other hand, Cole and MacCallum found the hemolytic streptococcus in all the twenty-six cases of empyema complicating their series of post-measles broncho-pneumonia at Fort Sam Houston.

TABLE 1.—The Results of Bacteriological Examination of Fifty Pleural Fluids Compared with Results for Eighty Fluids as Reported by Brooks and Cecil[5]

	Per Cent. of Our 50 Cases Showing the Organism		Per Cent. of Brook's and Cecil's 80 Cases	
Hemolytic streptococcus	52		53.7	
Sterile	22		18.7	
Pneumococcus Type I	6	22	2.7	18.7
Pneumococcus Type II			5.0	
Pneumococcus Type IV	16		10.0	
Nonhemolytic streptococcus	4		7.5	
Staphylococcus aureus	..		1.2	

In the study of etiology, a comparison of the bacteriology of chest fluid with the sputum in the same patient is important. Of twenty-seven instances in our series, in which organisms were determined in both fluid and sputum, seventeen, or 63 per cent., showed the same organisms, while ten, or 37 per cent., showed different organisms. Table 2 gives our findings in detail.

In the series of Brooks and Cecil 70.7 per cent. showed the same organism in fluid and sputum.

This brings up the question as to the value of the determination of sputum organisms in reflecting pulmonic or pleural infection. While the series of cases studied here is small, none the less, an inconsistency of about 35 per cent. in findings might be interpreted as a considerable factor of error. However, the manifold sources of origin of sputum and the mixture of infections so apt to occur in the respiratory tract should be considered.

From a study of our necropsy findings we hope to be able to show that mixed infections in the lungs account for the finding of one organism in the sputum and another in the pleural fluid. In our series, all empyemas developed during the acute stage of the broncho-pneumonia.

5. Brooks and Cecil: A Study of Eighty Cases of Empyema at Camp Upton, Arch. Int. Med. **22**:269, 1918.

Physical Signs of Pleural Exudate. — The study of the physical signs has been, as in Brooks and Cecil's series, very disappointing, and we also "have unlearned far more physical signs of pleural fluid than we have perfected." The diminished expansion of the base, the diminution, or loss of tactile fremitus, and most important, the flat percussion note still constitute the more reliable signs. Diminution of the breath and voice sounds and the ready audibility of râles are so misleading that we have learned to almost disregard them. Displacement of the heart has been inconstant. While the roentgen ray has been of immense aid in localizing the smaller pockets of fluid, there is no doubt that the presence or absence of fluid is best established by tapping, and numerous taps may be necessary.

TABLE 2.—Comparison of Bacteriology of Chest Fluid and Sputum in the Same Patient

Same Organism in Fluid and Sputum		Different Organisms in 10 Combined Examinations of Fluid and Sputum						
		Fluid			Sputum			
		Hemolytic Streptococcus	Nonhemolytic Streptococcus	Pneumococcus IV	Hemolytic Streptococcus	Nonhemolytic Streptococcus	Pneumococcus IV	Pneumococcus Undetermined
		2		1*		1* 2		
Hemolytic streptococcus	14	3 4†				4†		3
Pneumococcus I	2	5				5†		
Pneumococcus IV	1	6				6		
				7	7			
Total	17	9	8		8		9	
				10†		10		

* Numbers refer to the ten patients in this section.
† Indicates that the influenza bacillus was also found.

At the necropsy table an explanation was sought as to why the classical auscultatory signs of fluid were so often lacking. The answer to the question we believe is that whereas in the typical pleural effusions of tuberculosis or lobar pneumonia the lung is pushed up toward the hilus by the fluid, here the tendency toward sacculation is so strong that the lung very frequently is adherent over larger or smaller areas of the parietal chest wall, and we believe that lung tissue, so adherent and compressed by the surrounding fluid, makes an admirable conducting medium for the passage of breath and voice sounds.

The various and peculiar sacculations of the fluid at the base, between the lobes, between the pleura and pericardium, in the anterior mediastinum, etc., represent a later stage of this process of sacculation and render the localization of such fluid extremely difficult. The

encapsulation of these fluids was often beautifully shown by the roentgen ray, and was found by it to be more frequent than free fluid in large amounts.

Vaughan and Schnabel[6] have recently discussed the pathology and diagnosis of empyema in cases with and without an antecedent measles and have noted the tendency to the formation of pus pockets.

The treatment of these secondary infections largely concerns itself with the determination of the presence or absence of empyema. When pus is found we believe, with most of the recent writers, that operation should be delayed, not only in order that the pus may be well walled off, but that consolidated areas in the lung itself may be resolved as much as possible, so that the patient's general condition will be as favorable for operation as may be. With a continued typhoid-like temperature it is often very difficult to estimate whether its continuance is due to a persistent involvement of the lung or to pus. Afebrile empyemas are not uncommon. In such cases the pulse and respiration remain more rapid than in truly convalescent patients.

NECROPSY FINDINGS

Necropsy findings in the different periods of this epidemic varied considerably.

Douglass Symmers[7] has described the pathology of acute influenzal bronchopneumonia. We believe that capillary damage with resulting hemorrhages represents the keynote of the pathology and explains not only the wet, bloody, soggy lung seen at necropsy, but also the bleeding from nose, bowels or kidneys which occur clinically.

In this acute disease, the upper respiratory tract is acutely inflamed, the mucosa throughout being injected, swollen, succulent, with hemorrhages in places. The bronchial lymph glands are enlarged, and on cut section appear injected and hemorrhagic.

Pleural effusions, except for a small amount of sanguineous fluid in a few cases, were never found, and although the visceral pleura frequently lost its glossy sheen, fibrin in any considerable amounts was absent. The lungs were the site of the most important lesions: the involved lobes, especially the lower, presented a deep blue-red appearance and seemed bulky; while on palpation they were heavy and soggy, without, however, the solidity of pneumococcus hepatization. On section, the involved area was almost blue black and literally dripped a frothy, bloody fluid in large amounts, in marked contrast

6. Vaughan and Schnabel: Pneumonia and Empyema at Camp Sevier, Arch. Int. Med. **22**:440, 1918.

7. Symmers, D.: Note on the Pathology of Influenza, New York M. J. **108**:621, 1918.

to the "dryness" of lobar consolidation. No fibrin plugs came away with the knife. Areas of hemorrhagic infarction were fairly frequent. The anterior borders of the lungs were almost invariably emphysematous and uninvolved. A few cases showed some interstitial emphysema in the lung tissue, which led to a generalized subcutaneous emphysema in the three cases already mentioned under complications. Pneumothorax was found once.

In the less severe cases, only parts of lobes were involved and they appeared like the areas of marked congestion seen in hypostatic pneumonia. In the slighter involvements, patches of engorged or congested lung tissue were noted.

In these early acute cases the absence of pus deserves repeated emphasis. The pericardium was normal, the heart occasionally revealed a right-sided dilatation, which was, however, rarely marked. The endocardium was normal as was also the aorta.

The stomach and intestines occasionally revealed small areas of capillary hemorrhage in the mucosa. While the gallbladder was normal, the viscidity of the bile therein was markedly increased in a few cases to the consistency of thin paste. We believe that the flow of such bile can be retarded to the extent of producing an obstructive jaundice. Mere mention may be made of toxic degeneration in the liver, and the congestion of kidneys, spleen and brain.

Microscopic Study. — The alveoli and bronchioles contained an exudate composed mainly of red blood cells and serum; polymorphonuclear leukocytes with desquamated epithelial cells occurred to a lesser extent. Fibrin was not found.

In the areas of advanced disease, the structure of the alveolus was lost; large numbers of erythrocytes and a large amount of serum with a moderate number of leukocytes "packed" the alveoli and smaller bronchi. The capillaries were engorged and stood out. The bronchial walls were edematous.

In less advanced stages, the same cellular elements in the same proportion were found in lesser numbers and were at times grouped about the bronchi.

The heart muscle showed but slight granular degeneration. The kidneys showed considerable albuminous degeneration of the tubular epithelium, with granular debris in the lumina. The glomeruli were frequently congested.

The liver showed varying degrees of granular degeneration, the spleen, of congestion.

These findings indicate that the term "bronchopneumonia" is a misnomer, but in view of its general use, we hesitate to suggest a new term for this picture.

Secondary Bronchopneumonia.—With the advent of the secondary invaders, the pathology changed. Pus formation and the resemblance to post-measles bronchopneumonia were noted. The mucous membrane of the upper respiratory tract was bathed in a mucopurulent exudate, beneath which the mucous membrane was acutely inflamed. Edema of the glottis and ulceration of the vocal chords were seen.

The pleura in these cases showed the most important and most striking lesions. Larger or smaller areas of the visceral and parietal pleura were very often coated with a heavy, shaggy coat of fibrin, which by adhesions to the contiguous lung tended to form the pockets of pus which were so common. These encapsulated empyemas have not infrequently been multiple, in the positions already noted. It is of interest that often different pockets contained fluids of different color and consistency, ranging from a cloudy-amber to a greenish-yellow pus, and frequently showing shreds of fibrin.

The lungs revealed a condition of bronchopneumonia which can be divided into stages: first, beginning bronchopneumonia, where small reddened nodular areas stood forth on cut section, their center being a small bronchus which exuded pus, between which fairly normal crepitant lung was found; second, these same nodular areas became larger, grayish in color, and on pressure exuded considerable yellow pus from both bronchi and lung tissue; third, the spread and confluence of these areas produced a large area of consolidation—the pseudolobar bronchopneumonia of Osler,[8] and fourth, larger or smaller areas underwent necrosis with abscess formation, the affected tissue becoming soft, mushy, and losing its distinctive markings. Atelectasis and septic infarction need only be mentioned: the former common, the latter occasional.

The pericardium revealed not infrequently an acute serofibrinous inflammation: an acute vegetative endocarditis was seen but once; otherwise the heart and aorta were consistently "negative." The spleen in these cases was often enlarged, its pulp quite degenerated, mushy and necrotic.

The other viscera revealed no pathologic changes.

Microscopic Study.—In contrast to the hemorrhagic exudate of the former picture, the alveoli and bronchi in these cases contained an exudate of polymorphonuclear leukocytes and serum, whereas red blood cells were insignificant. The bronchial walls were edematous, infiltrated with polymorphonuclear leukocytes; their epithelium was frequently desquamated. While in less advanced areas polymorphonuclear cells were grouped about the bronchi, later this distinction was

8. Osler: Principles and Practice of Medicine, Ed. 8, Appleton Co., New York.

lost. In some of the specimens the number of large mononuclear (epithelioid) cells has been quite astonishing; these cells equaling, if not outnumbering, the polymorphonuclear leukocytes.

While actual giant cells were rarely seen in such specimens, a distinct tendency toward their formation was not infrequently noted.

Whether the presence of these large mononuclear cells is a part of cellular resolution indicative of a strong phagocytic process is problematical; however, the presence of a good many pigment-bearing cells in certain areas leads toward the belief that these mononuclear cells are capable of considerable phagocytic activity.

In certain cases edema was considerable.

TABLE 3.—A Comparison of the Bacteriology of the Lungs Between the First Fifteen and the Last Thirty of Forty-Five Consecutive Necropsies

	First 15 Cases From Sept. 23 to Oct. 8	Last 30 Cases From Oct. 9 to Nov. 18
Hemolytic streptococcus alone	0	10
Hemolytic streptococcus and pneumococcus	1	0
Hemolytic streptococcus, pneumococcus and influenza B.	1	3
Hemolytic streptococcus and influenza bacillus	2	6
Total hemolytic streptococcus	4 (26.4%)	19 (63.7%)
Influenza alone	3	0
Influenza and pneumococcus	5	4
Influenza and hemolytic streptococcus	2	6
Influenza, hemolytic streptococcus and pneumococcus	1	3
Influenza and nonhemolytic streptococcus	0	1
Total influenza	11 (72.6%)	14 (57.2%)
Pneumococcus alone	2	4
Pneumococcus and hemolytic streptococcus	1	0
Pneumococcus and influenza bacillus	5	4
Pneumococcus, hemolytic streptococcus and influenza B.	1	3
Total pneumococcus	9 (59.5%)	11 (34.3%)
Nonhemolytic streptococcus alone	1	2
Nonhemolytic streptococcus and influenza bacillus	0	1
Total nonhemolytic streptococcus	1 (6.6%)	3 (9.9%)

In the more advanced areas cells in various stages of degeneration, indicating necrosis, were found.

Our studies of the lungs of post-measles bronchopneumonia have not been extensive enough to allow of any comparison to their pathology, as described by Cole and MacCallum.

The kidneys and liver have shown extensive acute granular degeneration: the spleen, cellular necrosis with dilatation of the lymph spaces (producing the large mushy spleen).

Between the acutely engorged hemorrhagic lung of the pure influenza-bronchopneumonia, on the one hand, and this more advanced, less acute process associated with pus formation on the other, were

all stages of transformation and all combinations. In fact, in many of our cases, a mixed type of lung infection was found. The invasion by the secondary organisms is in no sense invariably productive of a pure type. We believe that this accounts for the discrepancy found on bacteriologic examinations of sputum and chest fluids. In measles, on the other hand, the invaders are almost invariably the hemolytic streptococcus, and as a consequence, a purer pathologic type of interstitial or lobular pneumonia is produced and the complicating empyema is naturally almost invariably due to the hemolytic streptococcus.

Bacteriology.—The bacteriologic findings in these lungs are shown in Table 3. Emphasis is to be laid on the fact that while the hemolytic streptococcus was found in only 26.4 per cent. of the first fifteen necropsies, in the last thirty it was found in 63.7 per cent. In contrast to this, the influenza bacillus was found in 72.6 per cent. of the first fifteen necropsies, and in 57.2 per cent. of the last thirty.

CONCLUSIONS

1. From our own observations and those of others, we believe that we are dealing with a severe, highly contagious, acute, infectious disease. As to the cause of this disease, we have been able to add nothing to the findings of others. The frequent finding of Pfeiffer's bacillus in sputa and in lungs at necropsy is interesting, but not peculiar to this disease.

2. We believe that we are dealing with one essential disease which at first is a clinical entity, but that the primary symptomatology and pathology is complicated in certain cases by changes due to secondary invading organisms. Our reasons are: first, the disease occurs in epidemic form; second, typical cases are clinically alike, and third, the clinical picture is distinct and is so characteristic of this disease as to differentiate it from that of any other disease.

3. It is our experience that all fatal cases develop "bronchopneumonia" before death, and we believe that this "bronchopneumonia" is but a later manifestation of pure influenza, because: first, the lung signs develop in many cases during the primary influenza; second, the pathologic picture of the lungs in influenzal bronchopneumonia is distinctly characteristic, being quite unlike the picture seen in other forms of pneumonia. We have referred to the misuse of the term "bronchopneumonia."

4. The later weeks of this epidemic were characterized by the invasion of numerous secondary organisms, among which the hemolytic streptococcus occurred in largest numbers. No one of these organisms occurred consistently enough to justify the assumption of a pure pathology. Furthermore, these invading organisms produced

a change in the clinical and pathologic picture of the individual case resulting in a mixed type of pulmonary lesion. The development, nature, and diagnosis of empyema as a complication was here characterized, not by free pus in the chest, but more often by the formation of pockets of pus.

5. The similarity between influenza, as observed here, and measles is striking. Both diseases occur in epidemic form and are very highly contagious. The clinical course is similar. Both diseases have a sudden onset, with fever high in degree and short in duration. In the acute stages, the upper respiratory symptoms, with coryza, lacrimation and an aggravating, unproductive cough are much alike. The occasional faint, evanescent rash in influenza is often suggestive of measles. Both diseases have a low total leukocyte count. The greatest similarity, however, lies in the predisposition of patients with, or convalescent from influenza, to develop secondary infections of the lung and pleura. Attention is called to this similarity in order to stimulate further study on the etiology of both diseases.

Our thanks are due to Major Edward S. Rimer for his interest, and to Capt. Raymond Sanderson and his laboratory staff for placing at our disposal laboratory data without which the writing of this paper would have been impossible.

LEUKOCYTIC STUDIES ON SOLDIERS WITH IRRITABLE HEARTS*

LESLIE N. GAY
First Lieutenant, M. C., U. S. Army
LAKEWOOD, N. J.

INTRODUCTION

This study of the morphology of the blood with reference to the leukocyte in cases of "irritable heart of soldiers" was suggested by the report of the Medical Research Committee, under the direction of Dr. Thomas Lewis.[1] In comparing this work to that which has been published in England, it must be borne in mind that the cases studied in the Hampstead Military Hospital may have differed from the type observed in U. S. Army General Hospital 9, at Lakewood, N. J. However, the basis of this work was a large series of selected cases in which no organic lesion of the heart and no foci of active infection were found by careful and repeated examination. The following are the more common symptoms given by these patients:

1. Breathlessness, produced by slight exertion.
2. Precordial pain, coming on suddenly after exertion, spreading over the left chest.
3. Fatigue, with or without exertion.
4. Vertigo, and occasionally fainting spells.

The studies here reported were undertaken in the following order:

1. A series of cases with "irritable hearts" was studied with no attempt at subdivision into special groups. The leukocytes were studied with reference to the number of cells; in addition a differentiation of the cells in the blood smear of each case was made by counting 200 cells.

2. A series of normal individuals, and a series of patients with organic heart lesions were used as controls. These were studied in a manner similar to the men with "irritable hearts."

3. The series of functional patients was then analyzed and each type was compared, one with the other. The classification used was based on a study of these patients made by Dr. C. Macfie Campbell.[2]

---

*From the Cardiovascular Service, U. S. General Hospital 9.

1. Lewis: Medical Research Committee, Special Report Series 8.

2. Campbell: J. A. M. A. **71**:1621, 1918.

4. Special observations on the morphology of the blood following the injection of epinephrin were also carried on in conjunction with the special studies in the reactions to epinephrin, the preliminary report of which has already been published.[3] Patients from the Surgical Service, ready for full duty, were used as controls.

5. The type of patient considered "constitutionally inferior" was selected for study to determine his reaction to exercise. Patients with organic heart lesions and those convalescent from rheumatic fever were chosen as controls.

For the differential studies the leukocytes were divided into the following groups:

1. Polymorphonuclear neutrophilic leukocytes (P. M. N.).
2. Polymorphonuclear eosinophilic leukocytes (P. M. E.).
3. Polymorphonuclear basophilic leukocytes (P. M. B.).
4. Lymphocytes, large and small (L. L., S. L.).
5. Mononuclears, large and small (M.).
6. Transitionals (T.).

1 and 2. *Study of General Group of "Irritable Heart" Cases and Controls.*—Two hundred and sixty counts were made on sixty-five patients to determine the number of leukocytes per cubic millimeter of blood. The procedure followed in each case was to have the patient rest for one hour before the blood was taken, and the puncture was made at least two hours after the ingestion of food. The possibility of a variation in the morning and afternoon counts was considered, and each patient was studied with this in mind. Two morning and two afternoon counts were made on each patient on different but not necessarily successive days. With one of the morning counts a blood smear was made by the coverslip method. The pipets were of the Leitz make and each had been checked for error. A Thoma-Levy hemocytometer was used.

Leukocytic Counts:	
Average of two a. m. counts on 61 patients	8,162
Average of two p. m. counts on 64 patients	8,450
Total average day count on 65 patients	8,290
Differential Counts:	
Average P. M. N. percentage of 74 patients	56.0
Average P. M. E. percentage of 74 patients	4.0
Average L. percentage of 74 patients	32.6
Small 31.0 Large 1.7	
Average M. and T. percentage of 74 patients	7.4
	100.0

3. Peabody, et al.: J. A. M. A. **71**:1912, 1918.

The results with the controls were as follows:

Leukocytic Counts:

Average of two a. m. counts on 12 organic cases	8,460
Average of two p. m. counts on 12 organic cases	8,740
Total average day count on 13 organic cases	8,400
Average of eight counts on eight normals	7,060
Total average count on 21 controls	7,900

Differential Counts:

	Thirteen Organics	Eight Normals
Average P. M. N. percentage	61.0	60.0
Average P. M. E. per centage	1.9	2.6
Average L. percentage:		
S.	26.0	25.0
L.	2.4	2.0
	28.1	27.0
Average M. and T. percentage	9.0	11.4
	100.0	100.0

TABLE 1.—COMPARISON OF THE LEUKOCYTIC COUNTS IN PATIENTS AND CONTROLS

	Leukocytes, Average	Differential Formulas—P. M. N. Per Cent.	P. M. N. No.	P. M. E. Per Cent.	P. M. E. No.	Lymphocytes Per Cent.	Lymphocytes No.
"Irritable hearts"	8,290	56.0	4,642	4.0	332	32.6	2,702
Organic hearts	8,400	61.0	5,124	1.9	160	28.1	2,360
Normal controls	7,060	60.0	4,236	2.6	184	27.0	1,906
Miller's normal average	7,705	63.5	4,895	2.7	218	21.9	1,724

DISCUSSION

The variation in these cases is seen by a comparison of the accompanying tables and charts. There is no appreciable difference in the leukocyte counts of the Organics and the Functionals; in fact, the former show averages slightly above the latter. The normal controls show averages 1,000 cells below either of the series of patients. The averages of Miller[4] for normals show a less marked difference. It may be concluded that the leukocytes of "irritable heart" patients are slightly increased above the normal, but only to a small degree. In both controls and patients the morning counts average lower than the afternoon, which finding is a normal reaction. The high leukocytosis which Lewis mentioned in his report has not been present in the average of the patients studied in this hospital. The highest count in the "irritable heart" patients was 16,350; the lowest count was 4,700. In the controls the counts varied between 12,300 and 4,500.

From the percentages obtained from counting 200 cells in each smear preparation, the absolute values of the various leukocytes per

4. Miller: Johns Hopkins Bull. **25**: 1914.

cubic millimeter of blood were calculated, using as a basis the total day average count. A comparison of the differential results shows that there is a relative lymphocytosis and a decrease in the polymorphonuclear neutrophilic cells in the functional cases. In the controls the figures for the organic cases and the normal individuals are practically the same. The formulas of the controls correspond to the figures determined by Miller.[4] His figures are tabulated for comparison in Table 1. An eosinophilia was present in all but sixteen patients of this series. The exceptions had a normal percentage. The limits of the eosinophilia ranged from 13 per cent. to 1.5 per cent.

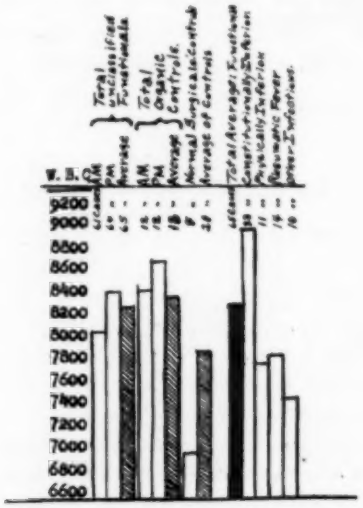


Chart 1.—General comparison of leukocyte counts.

3. *Analysis of the "Irritable Heart" Group.* — The classification used is based on the general suggestions given by Dr. C. Macfie Campbell. Four clinical types have been considered:

1. Constitutional Inferiority. This term is used in a very broad sense to cover a very heterogeneous group.

2. Physical Inferiority. Separated from the general group of Constitutional Inferiors because of its prominence by numbers among the other types.

3. Postrheumatic Type. Soldiers with a definite history of at least one attack of rheumatic fever without discoverable organic findings.

4. Postinfection Type. Soldiers convalescing from some infection other than rheumatic fever without organic findings.

The average total counts and the differential formulas of these types are shown in the tables and charts. (Table 2 and Charts 1 and 3.)

TABLE 2.—Comparative Findings in the Types of "Irritable Heart"

Type	Cases No.	Leukocytes No.	P. M. N. Per Cent.	P. M. N. No.	P. M. E. Per Cent.	P. M. E. No.	Lymphocytes Per Cent.	Lymphocytes No.
Constitutional inferiors..	32	9,000	55.0	4,950	3.8	342	32.0	2,880
Physical inferiors.....	11	7,800	58.0	4,524	4.0	312	31.4	2,465
Postrheumatic.....	13	7,900	52.0	4,108	4.0	316	36.5	2,884
After other infections.....	8	7,500	60.0	4,500	3.7	276	29.0	2,175

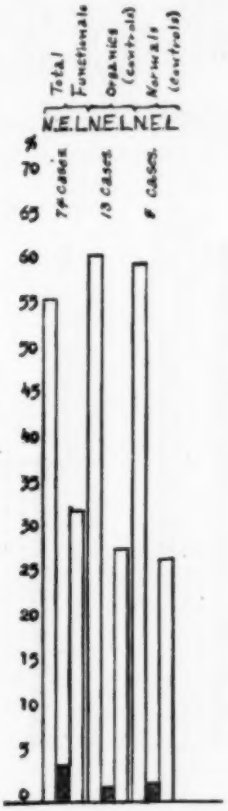


Chart 2.—Comparison of differential counts in "Irritable Hearts," Organic Heart Disease and Normal Controls. N, polymorphonuclear neutrophils; E, polymorphonuclear eosinophils; L, large and small lymphocytes.

In the general Constitutional Inferior Group, the highest leukocytic count was 13,350, and the lowest was 6,000. With the exception of three cases out of a total of thirty-two of this type the white cell count

was above 8,000 cells. The other groups have normal counts. No evidence is found of any direct proportion in leukocyte increase to the severity of the symptoms. In the differential counts the absolute number of cells closely corresponds in all types of the cases.

4. *Studies on the Blood Morphology after Epinephrin Injection.*—The controls used in the blood studies in these observations were

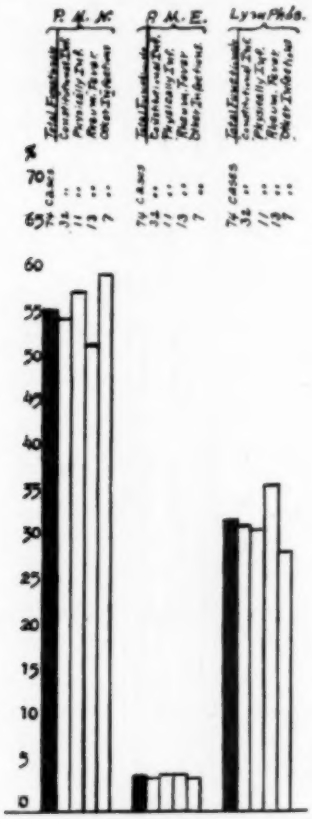


Chart 3.—Comparison of differential counts in four types of "Irritable Hearts."

patients on the Surgical Service, who gave no "effort syndrome" symptoms and gave no reaction after the injection of epinephrin. In each case, with controls and subjects, the patient was placed at rest in bed for one hour previous to the epinephrin injection. At the end of this hour the first specimen of blood was taken. Then 0.5 c.c. of a 1:1,000 solution of epinephrin chlorid was injected intramuscularly. At the height of the reaction in the "epinephrin positive" cases,

and at the end of thirty-five minutes in the negative cases, a second specimen of blood was taken. At the end of an hour, when all the reaction symptoms had subsided, a third specimen was taken. From each of these three specimens leukocytic and differential counts were made. The same pipet was used for each of the three specimens of each individual case in order to avoid any possible error that could be made constant.

TABLE 3.—LEUKOCYTIC COUNTS AFTER EPINEPHRIN INJECTION

	Number Cases	Reaction	After First Hour	At Height of Reaction	After Quiescence
Controls	12	Neg.	8,671	11,100	8,425
"Irritable heart"	16	Pos.	7,812	11,525	8,181

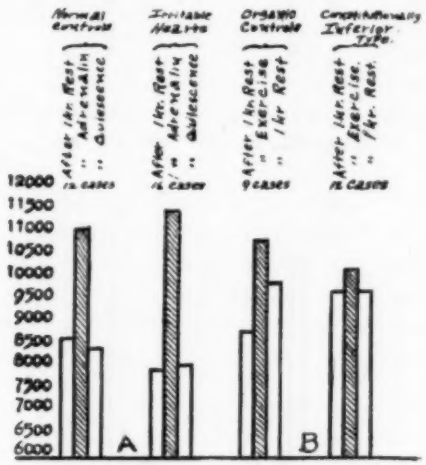


Chart 4.—A. Comparison of leukocytic increase from injection of epinephrin. B. Comparison of leukocytic increase from physical exercise.

TABLE 4.—DIFFERENTIAL STUDIES AFTER EPINEPHRIN

	After Rest				After Epinephrin				After Quiescence			
	P. M. N.		Lymphos.		P. M. N.		Lymphos.		P. M. N.		Lymphos.	
	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.
Controls	50	5,116	26	2,254	53	5,883	31	3,441	58	4,886	29	2,443
Subjects	60	4,687	30	2,344	58	6,684	29	3,342	62	5,072	27	2,209

In both patients having a positive reaction to epinephrin, and in the controls with a negative reaction there was a marked leukocytosis after a period of thirty minutes following the injection of the drug. The percentage of increase in the patients was 47.5, while the percentage in the controls was 28.1. Whether this more marked increase in the patients would also be found in cases of "irritable heart" that do not show a positive reaction to epinephrin has not been determined.

The eosinophil cells were not charted because no variation was found, there being a normal eosinophil count in the controls and a high eosinophilia in the patients before and after the injection of epinephrin.

5. *Blood Morphology in the Type Constitutional Inferior After Exercise.*—A group of patients with organic heart disease was chosen as controls in this study. The subjects were cases of definite "constitutional inferiority." Both controls and subjects were given the same exercises for a period of twenty minutes.

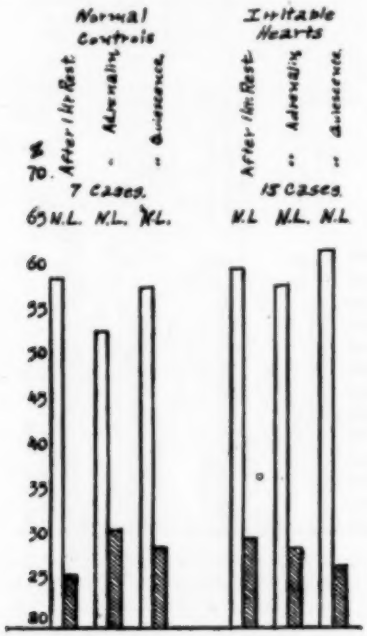


Chart 5.—Comparison of differential counts. Normal Controls, epinephrin negative; Irritable Heart cases, epinephrin positive. Specimens taken at the same time intervals as in Chart 4.

TABLE 5.—Leukocytic Counts Before and after Exercise

	Case Number	After 1 Hour of Rest	After Exercise	After 1 Hour of Rest
Controls	9	8,870	10,800	9,960
Subjects	12	9,730	10,240	9,740

The subjects show a leukocyte increase of 5.2 per cent. after the exercise, compared with 22.7 per cent. shown by the controls. This difference is explained by the lack of "push" in the inferior type.

They do not make enough effort to cause a normal reaction. Further observations were interrupted by the transfer of the writer to another station.

SUMMARY

1. There is a slight leukocytosis in the unclassified group of patients with "irritable heart." The figures in this correspond, however, to those found in the patients with organic heart disease.

2. The type of patient classed as "Constitutional Inferior" has a high leukocytic count. The other types studied have a normal count.

3. There is a relative lymphocytosis present in the blood of patients with "irritable heart," the limits being between 15 and 51 per cent. An eosinophilia is likewise present, but too much importance cannot be given to this finding, since the presence of parasites was not ruled out.

4. A marked leukocytosis occurs in both patients and controls after the injection of epinephrin. This increase is much greater in the patients with positive reaction than in the controls, who did not respond to the drug.

5. There is no greater variation in the differential formulas after the injection of epinephrin than was to be found before. The eosinophilia persisted in about the same proportion as before.

6. The morphologic studies of the blood in cases of "irritable heart" show nothing of significance that might assist in the diagnosis.

THE INFLUENCE OF FASTING AND VARIOUS DIETS ON THE LIVER INJURY EFFECTED BY CHLOROFORM ANESTHESIA*

PAPER I

N. C. DAVIS AND G. H. WHIPPLE, M.D.
SAN FRANCISCO

As an introduction to a study of liver injury due to chloroform anesthesia, it is necessary to understand clearly how uniform is the individual reaction to this drug under uniform conditions. We submit data in the following papers sufficient to convince a sceptic that the liver injury in a given dog will be uniform in extent provided the intake of food is accurately controlled and the dog is in good clinical condition. The evidence shows that a unit injury due to a unit chloroform anesthesia under fasting conditions will be repeated accurately again and again, provided the dog is given sufficient time to repair each injury to normal. This gives us much confidence in the interpretation of results and enables us to draw finer distinctions in type and extent of injury. In a review of the literature it will be noted that there is the greatest amount of variation in the recorded susceptibility of dogs to chloroform, but little if any data are given to show the *diet conditions* which we feel sure would explain the remarkable discrepancies.

We sometimes record unusual individual resistance or hypersusceptibility to chloroform poisoning in these experiments, but such exceptions are rare and obtain in all physiologic or pharmacologic experiments. When a sufficient number of experiments are submitted the law of reaction may be established and the few individual exceptions put aside for later consideration. It is truly remarkable to note the uniformity of the liver injury which follows a suitable unit period of chloroform injury given to a dog after three or four days of fasting. Under these conditions the dog is the ideal subject for a study of chloroform injury and repair.

REVIEW OF EXPERIMENTAL WORK

Delayed chloroform injury has been reported occasionally since about 1850, sometimes diagnosed correctly, often called a postoperation acidosis or toxemia of unknown etiology; sometimes called acute yellow atrophy when necropsy material was available. Experimental

*From the George Williams Hooper Foundation for Medical Research, University of California Medical School.

work began in the latter half of the nineteenth century. Strassman,[1] in 1889, determined, among other things, that hemorrhage made dogs more susceptible to injury. In 1905, Bevan and Favill[2] carefully reviewed the literature, both clinical and experimental, and pointed out that diabetes, hemorrhage, and wasting diseases predispose to injury. In an able article in 1908, Wells[3] expressed the belief, postulated by others, that previous liver injury favors a severe chloroform reaction; he also mentioned the fact that sugar feeding is protective against phosphorus poisoning, and presumably would be protective against chloroform injury, also, since the liver can readily use sugar, but protein and fat less easily. He has suggested[4] that sugar by its antiketonic action tends to maintain cell neutrality, thus preventing acidosis and death. In 1909, Howland and Richards[5] again reviewed the question of delayed chloroform poisoning, with especial reference to metabolic disturbances. In 1909, Whipple and Sperry[6] followed experimentally the lesions in various organs, caused by chloroform administration, and gave an excellent histologic picture of the liver injury and repair.

In 1910, Foster[7] studied the influence of different proportions of protein in the food on resistance to the toxicity of ricin, and on recuperation from hemorrhage. He considered the results with ricin unsatisfactory; and concluded that the resistance to hemorrhage is determined more by breed of dog and individual idiosyncrasies than by total amount of food or amount of protein taken. Hunt[8] made observations on the effects of a restricted diet and of various diets on resistance of animals to certain poisons, principally acetonitril. Mice or guinea-pigs were used in most experiments. He found that feeding thyroid gland, or blood from cases of hyperthyroidism, conferred a marked resistance to the drugs and decided that other diets had good or bad effects through their influence on the thyroid gland of the recipient. Certain diets, notably dextrose, oatmeal, liver and kidney, greatly increased resistance to acetonitril. Eggs, cheese, milk and various fats greatly lowered resistance. Prostate, ovary and testis acted simlarly to, but less markedly than thyroid; thymus, parathyroids and adrenals either had no effect, or one opposite to thyroid. A

1. Strassman: Virchow's Arch. f. path. Anat. **115**:1, 1889 (Cited by Bevan and Favill, Footnote 2).

2. Bevan, A. D., and Favill, H. B.: J. A. M.A. **45**:691, 1905.

3. Wells, H. G.: Arch. Int. Med. **1**:589, 1908.

4. Wells, H. G.: Chemical Pathology, Ed. 3, Saunders & Co., 1918.

5. Howland, J., and Richards, A. N.: J. Exper. M. **11**:344, 1909.

6. Whipple, G. H., and Sperry, J. A.: Bull. Johns Hopkins Hosp. **20**:1, No. 222, 1909.

7. Foster, N. B.: J. Biol. Chem., **7**:379, 1910.

8. Hunt, Reid: Hyg. Lab. Bull., 1910, No. 69.

restricted diet usually gave more resistance than either overfeeding or starvation.

Whipple[9] found that pups, during the first three weeks of life, are very insusceptible to chloroform injury, and suggested a correlation between this phenomenon and the presence in these young animals of persisting cell nests of blood forming elements, although it was not known what neutralizing action they could exert. Mosiman and Whipple[10] also found that the pigeon, frog and terrapin are extremely resistant to chloroform. It is interesting that these animals have nucleated red blood corpuscles. Graham[11] has maintained that the resistance of pups is due to the high content of glycogen in their livers, and obtained the typical injury after a short preliminary starvation, or starvation and phlorizin. Adult animals were also rendered more resistant by preliminary sugar feeding. A similar explanation has not been offered for the insusceptibility of birds, reptiles and amphibians. Nutritional analyses[12] show a carbohydrate content in the livers of the chicken, turkey and goose, which is quite comparable to that in mammalian livers.

In 1914-1915 Opie and Alford[13] published articles on the influence of diet on the hepatic lesions of chloroform, phosphorus or alcohol, and on the nephritis caused by potassium chromate, uranium nitrate or chloroform. Rats were used as experimental animals; chloroform was given subcutaneously. Susceptibility to all poisons was found to be less after a rich carbohydrate diet. The toxicity of chloroform and uranium nitrate was greatest after a fat diet; that of phosphorus was greatest after a meat diet. Brain and egg yolk, containing lecithin, cholesterol, etc., apparently predisposed to injury similarly to fat. Fat mixtures were less efficacious as diets than the combinations minus fat. The conclusion was drawn that the great solubility of fat in chloroform, and the relative fixation of chloroform by the body fat and watery fluids, determines the increased susceptibility of animals which have received fat and stored it in the parenchymatous cells of the liver and kidney; factors of location must not be overlooked, since all fatty tissues are not necrotized.

McDanell and Underhill[14] have shown that in rabbits a base-forming diet, such as carrots, is somewhat more efficient than an acid-forming diet, such as oats, in the formation of liver glycogen. Early

9. Whipple, G. H.: J. Exper. M. **15**:359, 1912.
10. Mosiman, R. E., and Whipple, G. H.: Bull. Johns Hopkins Hosp. **23**:1, No. 261, 1912.
11. Graham, E. A.: J. Exper. M. **21**:185, 1915.
12. Bull. 28 (Revised), Office of Experiment Stations.
13. Opie, E. L., and Alford, L. B.: J. A. M. A. **62**:895, 1914; J. Exper. M. **21**:1, 1915.
14. McDanell, L., and Underhill, F. P.: J. Biol. Chem. **29**:255, 1917.

in 1918 Salant and Swanson[15] published their observations on the influence of diet on the toxicity of sodium tartrate, and on the nephritis caused by sodium tartrate, as measured by renal function tests. Cats, rabbits and rats were used as experimental animals. In cats a decreased resistance was found with starvation, and with meat feeding. Carbonates increased resistance, perhaps by a relief of acidosis caused by organic acids. Resistance of rabbits was the same on starvation, and on acid or alkaline diet. Toxicity of sodium tartrate was greatest on a diet of oats, hay and cabbage. Diets rich in sugar were efficacious in decreasing toxicity, the most pronounced being carrots; carrot leaves were also good. It was suggested that the favorable effect may be due to several factors, such as: inhibition of bacterial activity in the intestines; vitamins; or other unknown constituents of the diet.

Very recently Simonds[16] has reported that sugar feeding to normal animals seems to have no effect on the ereptic power of organs, but feeding sugar before and after phosphorus poisoning apparently prevents the reduction of the ereptic power of the liver, which usually takes place after phosphorus injection.

The picture of chloroform injury, described by so many workers, seems to depend, therefore, not only on the amount of chloroform administered, but on the subject's previous nutrition as well. The milder injuries usually cause more or less fatty change in the liver; the more intense injuries produce actual necrosis. The typical chloroform necrosis affects the centers of the liver lobules, showing from six to ten hours after administration of the drug. The dead area usually appears hyaline, and quite homogeneous for from twenty-four to forty-eight hours. Wandering cells then make their appearance and aid the tissue ferments in removing the necrotic mass between the second and fifth days, in cases of recovery. During the process of dissolution the neighboring, intact liver cells begin to proliferate; mitoses become numerous; cell strands extend in to occupy the stroma recently filled by dead material. Even under favorable conditions there is usually a period between the removal of debris, and final repair, when a certain amount of collapse of unfilled stroma is to be seen surrounding the central veins.

Taylor,[17] and later, Wells,[18] have shown by chemical analyses of livers from fatal, human cases of chloroform poisoning, that there is a high amino-acid and fat content.

---

15. Salant, W., and Swanson, A. M.: J. Pharm. and Exper. Therap. **11**:43, 1918.
16. Simonds, J. P.: J. Exper. M. **28**:673, 1918.
17. Taylor, A. E.: Univ. Calif. Pub. (Pathol.), **1**:43, 1904.
18. Wells, H. G.: J. Biol. Chem. **5**:129, 1908-1909.

In this communication we are presenting the results of some feeding experiments corroboratory of Opie's work on rats, which bring out a few new and interesting points.

METHODS

Young dogs and pups were used, principally, as experimental animals; a few older, adult, dogs were utilized; rats, also, were used in some experiments. Feeding of special diets usually lasted from three to six days, the exact time being indicated in the individual protocols. Data has accumulated on numerous starvation controls, but to avoid repetition only a limited number of these records are indicated in our tables. In most cases food has been left in the cages for the dogs; pups eat special or limited diets more readily than the older dogs. Fluids, such as cottonseed oil, sugar solution, beef extract solution, etc., have been given by stomach tube.

Dogs have been anesthetized with chloroform (either Squibb's, or Powers-Weightman-Rosengarten Co.'s U. S. P. products) by the drop method for definite time intervals; rats have been chloroformed in groups in an improvised gas chamber; a relatively light anesthesia has been deemed sufficient in all cases. Pups have been anesthetized for one hour; older dogs which were starved only three days have usually been given one and one-half hours, those starved four days being given one and one-fourth hours. Young dogs show a more uniform reaction under standard conditions than do old dogs.

Operations have always been performed under ether anesthesia, with all aseptic precautions. This has not always prevented postoperative infection. Moreover, it has often seemed that the operative wounds have a tendency to open superficially because of imperfect reparative processes, associated with the limited diets. The operative procedure itself is very simple. A laparotomy is done and either a tip of one of the projecting smaller lobes is ligatured and snipped off, or a mattress suture is put in one of the larger lobes a short distance from the margin, tightened, and a small wedge of tissue removed from the area where the blood supply is shut off. Fixation has been in formaldehyd solution; material has been divided for frozen sections, with fat staining, and for imbedding, with later hemotoxylin and eosin staining.

In cases in which animals have been sacrificed, ether anesthesia has been used, and death accomplished by exsanguination. In such cases sections have been procured from other organs besides the liver.

There may be a criticism that a section from the edge of the liver does not fairly indicate the injury toward the center of the lobe, or in other lobes. It is true that the liver parenchyma underlying the capsule does show a more severe injury than an equal strip through the center of a lobe; however, this layer is very thin, and even in the smallest sections which we have removed it is always possible to find many lobules which are fair representatives of the interior. With necropsy material it has always been our custom to obtain sections from various locations, and these always present practically the same picture. When dogs die a few hours after operation, the operative and necropsy material invariably show the same amount of injury.

It may be noted that in certain instances we have used the same dog for several experiments. We have found, as did Opie, Barker and Dochez,[19] that dogs which survive an initial chloroform injury may be given chloroform thereafter on successive or alternate days for a week

19. Opie, F. L., Barker, B. I., and Dochez, A. R.: J. Exper. M. **13**:162, 1911.

or two without increasing the original necrosis, although the liver may become intensely fatty and the animal very much jaundiced and intoxicated. Quinan[20] also mentions this phenomenon of chloroform tolerance If the dog is allowed to recover for two or three weeks, however, a tolerance to a second dose is not exhibited. As has been already mentioned, Wells and others have thought that a previous liver injury is a predisposing factor in subsequent chloroform injuries. We have found no indication of such action in our dogs. While we have tabulated no experiments to prove, or disprove, this point, a perusal of the experiments in this and the following papers will indicate that successive injuries following equal doses of chloroform are comparable, other factors being equal.

EXPERIMENTAL OBSERVATIONS

Table 1 briefly presents the results of a number of feeding experiments with carbohydrates, fat alone, and mixtures containing a considerable amount of fat as one constituent. Representative protocols of experiments here tabulated immediately follow.

TABLE 1.—CARBOHYDRATE FEEDING; STARVATION; FAT FEEDING

Experiment	Diet	Chloroform	Liver Injury		Remarks
			Central Necrosis	Fat	
1 (Pup 3c)	Carbohydrate (sugar, rice, potatoes, etc.)	1 hr.	0	1/3; slight and diffuse	Blood urea low
2 (Pup 4e)	Corbohydrate (sugar, rice, potatoes, etc.)	1 hr.	0	2/3; scattered	
3 (Adult 19-34)	100 gm. sugar daily; 5 days	1¼ hr.	1/2-3/5	1/3; heavy	
	Starvation 4 days (control)	1¼ hr.	3/4	Heavy to periphery	Operated on: hemorrhage uncontrollable; hemorrhage + liver injury fatal
4 (Pup 3b)	Starvation 4 days (control)	1 hr.	4/5	Moderate throughout	Fatal injury
5 (Pup 3c)	Fat (butter, lard, fat meat)	1 hr.	1/3	4/5; heavy	
6 (Pup 4b)	Fat (butter, lard, fat meat)	1 hr.	3/4	Heavy to periphery	Fatal injury; fibrin low; blood urea very high; calcium deposits in liver
7 (Pup 4c)	Fat and carbohydrate (lard, butter, fat meat, rice and potatoes)	1 hr.	1/2	1/2; heavy zone about necrosis	Blood urea very high
8 (Pup 5e)	Fat and carbohydrate (lard, butter, fat meat, rice and potatoes)	1 hr.	3/4	Heavy to periphery	Blood urea high
9 (Pup 19-56)	Skeletal muscle and fat	1 hr.	1/2	1/3; moderate	

20. Quinan, C.: J. M. Res. **32**:73, 1915.

EXPERIMENT 2.—*Carbohydrate Diet.*—Pup 4 e, a black female mongrel.

May 23: Isolated; starvation; pup is 2 or 3 months old; bright and active.

May 24: Wt., 5.88 lbs. Feeding begun; food consists of potatoes, rice, cracker meal and sugar, *ad. lib.;* eaten well.

May 25: Wt., 5.96 lbs. Food eaten well.

May 26: Wt., 5.88 lbs. Food eaten well.

May 27: Wt., 5.7 lbs. *Chloroform for 1 hour* (from 9:40 to 10:40 a. m.).

May 28: Wt., 5.5 lbs. Eats very little; continues active.

May 29: Wt., 5.25 lbs. Sacrificed in a. m.; blood urea, 25 mg.; urea N., 12 mg.; fibrin, 260 mg. per 100 c.c. plasma.

Necropsy Report.—Blood does not clot quite as readily as normal. Liver: Weight, 74 gm.; no necrosis apparent; looks fatty, however; remaining viscera negative.

Microscopic Report.—Liver: No necrosis; central two thirds of each lobule contains a small amount of diffuse fat in very small droplets.

EXPERIMENT 3.—*Sugar Diet.*—Dog 19-34; adult, brown and white male terrier.

Oct. 10: Wt. 16.6 lbs. Isolated; recovering from distemper; one eye still sore; very active; sugar by stomach tube: 75 gm. cane sugar, 25 gm. glucose, and kaolin.

Oct. 11: Wt. 16.38 lbs.; Oct. 12, Wt., 16.13 lbs.; Oct. 13, Wt., 15.75 lbs.; dog continues active; 100 gm. sugar daily.

Oct. 14: Wt., 15.75 lbs. Sugar in a. m. *Chloroform for one and a quarter hours* (from 2 to 3:15 p. m.).

Oct. 15: Wt., 15.2 lbs. Bright and active; no food.

Oct. 16: Wt., 14.8 lbs. Bright and active; no food. *Piece of liver removed* at 4 p. m.; necrosis one half to three fifths; fat + +.

Oct. 17: Full diet; mixed food.

Oct. 19: Eats all right; distemper entirely gone; wound satisfactory.

EXPERIMENT 3.—*Starvation (Control).*—Dog 19-34 (continued).

Oct. 28: Wt., 16.25 lbs. Isolated for starvation (before daily feeding); active and in good condition; wound practically all healed.

Oct. 29: Wt., 15.5 lbs.; Oct. 30, Wt., 15.25 lbs.; continues active; no food.

Oct. 31: Wt., 14.7 lbs. Lively and in good condition. *Chloroform for one and a quarter hours* (from 1:10 to 2:25 p. m.).

Nov. 1: Wt., 14.3 lbs. Still very active.

Nov. 2: Wt., 14.13 lbs. Active. *Piece of liver removed* at 10:30; excessive bleeding.

Nov. 3: Found dead.

Necropsy Report.—Much free blood in peritoneal cavity; liver shows no normal tissue; extensive necrosis and fat; duodenum injected.

Microscopic Report.—Liver shows three fourths or more necrosis; remainder fatty. There seems to be a slight removal of debris between operation and death. *Kidneys:* cloudy swelling. *Spleen:* hemorrhage.

EXPERIMENT 4.—*Starvation (Control).*—Pup 3 b, a black female mongrel.

May 14: Isolated. This pup was chosen for starvation because the heaviest in the litter, and in excellent condition.

May 15: Wt., 6.25 lbs.; May 16, Wt., 6 lbs.; May 17, Wt. 5.7 lbs.; no food.

May 18: Wt., 5.56 lbs. *Chloroform for one hour* (from 10:30 to 11:30 a. m.); *no food.*

May 19: Wt., 5.2 lbs. The pup was noisy but lively even after chloroform; *no food.*

May 20: Wt., 5.06 lbs. Found dead.

Necropsy Report.—Blood is not clotted, and refuses to clot on contact with tissues (autolysis?). *Thymus:* shows many ecchymoses. *Lungs:* one dark area (probably hypostasis) in left lower lobe. *Liver:* weight, 109 gm. The lobule centers are large and dark and are surrounded by light opaque zone extending almost to the peripheries, leaving very little normal, translucent tissue. *Duodenal mucosa:* slightly injected; no hemorrhages.

Microscopic Report.—Thymus: congestion and some hemorrhage. *Lungs:* congestion; no hemorrhage. *Liver:* about four fifths necrotic. Fat ++. *Kidneys:* slight cloudy swelling.

EXPERIMENT 6.—*Fat Diet.*—Pup 4 b, a brindle male.

May 23: Isolated; starvation; pup is 10 weeks old; bright and active.

May 24: Wt., 6 lbs. Feeding begun; diet consists of lard, butter and bits of fat from garbage can, mixed with a very little cracker meal.

May 25: Wt., 6.38 lbs.; May 26, Wt., 6.3 lbs.; *fat* eaten with a good appetite.

May 27: Wt., 6.25 lbs. *Chloroform for one hour* (from 10:50 to 11:50 a. m.).

May 28: Wt., 5.8 lbs. No food touched since anesthesia; sick; very thirsty; vomits; sacrificed at 4 p. m.; blood urea, 101 mg.; urea N., 47 mg.; fibrin, 94 mg. per 100 c.c. plasma.

Necropsy Report.—Blood not clotted after a half hour contact with tissues. *Liver:* weight, 148 gm. Lobules about four fifths a dull pink; opaque and yellow to peripheries. *Spleen:* mottled brown and purple; malpighian bodies very large and milky.

Microscopic Report.—Liver: about three fourths necrosis, totally unresolved; almost all of remaining cells are extensively vacuolated with fat; fat also extends into necrotic area; some masses in the necrosis suggest calcium deposits. *Kidneys:* a little cloudy swelling. *Spleen:* hyperemic.

EXPERIMENT 8.—*Fat and Carbohydrate Diet.*—Pup 5c, a black spaniel, male.

June 3: Isolated; starvation; pup is 6 weeks old; healthy and active.

June 5: Wt., 6.25 lbs. Feeding begun; fat and carbohydrate in approximately equal parts; fat = butter, lard and bits of fat meat from garbage. Carbohydrate = rice and potatoes. Food *ad lib.*

June 6: Wt., 6.13 lbs. Food same as yesterday; does not eat very much.

June 7: Wt., 6 lbs. Added 30 c.c. cottonseed oil and 30 gm. sugar to diet.

June 8: Wt., 5.96 lbs. Sugar and oil as yesterday (by stomach tube). *Chloroform for one hour* (from 10:25 to 11:25 a. m.).

June 9: Wt., 5.56 lbs. Sugar and oil again; vomited.

June 10: Wt., 5.63 lbs. Quite sick; sacrificed in a. m.; blood urea, 81 mg.; urea N., 38 mg.; fibrin, 140 mg. per 100 c.c. plasma.

Necropsy Report.—Liver: weight, 116 gm. Gross appearance of about one half necrosis, and fat practically to periphery of lobules.

Microscopic Report.—Liver: about three fourths necrosis; all more or less fatty. *Kidneys:* slight congestion and cloudy swelling.

EXPERIMENT 9.—*Fat and Lean Meat Diet.*—Dog 19-56, a female, collie pup.

Nov. 3: Wt., 7.06 lbs. Isolated for feeding; previously given beef extract, then chloroform and regeneration on kidney diet; wounds in good shape. 100 gm. *skeletal muscle* + 100 gm. *fat* from beef hearts.

Nov. 4: Wt., 6.8 lbs. Ate some of yesterday's food; 75 gm. *meat* + 75 gm. *lard.*

Nov. 5: Wt., 6.8 lbs.; Nov. 6, Wt., 7.13 lbs.; 75 gm. *meat* + 75 gm. *lard* daily; eats well.

Nov. 7: Wt., 6.8 lbs. *Fat* and *meat.* Chloroform for one hour (from 3:05 to 4:05 p. m.).

Nov. 8: Wt., 6.75 lbs. Mixed food. Eats some. Rather quiet.
Nov. 9: Wt., 6.56 lbs. Sacrificed at 11 a. m.

Necropsy Report: Liver is pale, yellowish, opaque—probably fatty throughout— with distinct lobule centers, representing undoubted necrosis of one third or more. Other organs negative.

Microscopic Report: Liver: about one half necrotic; fat ++. *Spleen:* malpighian bodies enormous.

Experiments 1 and 2 illustrate very well the resistance to chloroform exhibited by pups previously fed a carbohydrate diet. The contrast between the injury sustained by these pups and by the control on starvation (Experiment 4) is very striking. Experiment 3 may appear atypical, but it must be realized that this was an adult dog receiving only 100 gm. of sugar daily, and that this amount lessened the injury which might have been expected (compare control) and undoubtedly saved the animal's life in the first instance. Apparently, the dog was very susceptible to chloroform injury. It will be observed that in Experiments 5 to 9, where fat is a feature of the diet, the injury conforms to the type obtained after starvation. There seems to be a slight resistance in some cases, but, in general, it must be concluded that fats, and food combinations containing fat in large amounts are not protective. Furthermore, when it is considered that large amounts of protective carbohydrate fail to prevent the bad effect of the fat quota in a mixture, it would appear that a negative value should be attached to fats; that is, they are not only not protective against chloroform injury, but are actually harmful. These results corroborate the work of Opie on rats. It may be mentioned that we have also found that rats fed on fat are very susceptible to chloroform injury.

TABLE 2.—Feeding of Brain and Parenchymatous Organs

Experiment	Diet	Chloroform	Liver Injury		Remarks
			Central Necrosis	Fat	
10 (Pup 19-44)	Brain and cracker meal	1 hr.	0	0	
11 (Pup 19-44)	Brain	1 hr.	Trace	0	Died from distemper a few hours after chloroform; hardly time for necrosis to show well
12 (Pup 19-81)	Brain	1 hr.	0	0	
13 (Pup 19-88)	Brain	1 hr.	Trace	0	A few focal necroses
14 (Pup 19-43)	Kidney	1 hr.	0	0	
15 (Pup 5d)	Liver	1 hr.	Trace	3/4; intense in central 1/3	
16 (Pup 3f)	Liver	1 hr.	0	Trace	Blood urea very high; fibrin high

EXPERIMENT 12.—*Brain Diet.*—Dog 19-81, a female Airdale pup.

Nov. 27: Wt., 11.9 lbs. Isolated for feeding; very active; skinny; 400 gm. *brain.*

Nov. 28: Wt., 11.3 lbs.; 400 gm. *brain;* all eaten.

Nov. 29: Wt., 10.75 lbs.; Nov. 30, Wt., 10.63 lbs.; Dec. 1, Wt., 10.44 lbs.; Dec. 2, Wt., 10.25 lbs.; 500 gm. *brain* daily; all eaten.

Dec. 3: Wt., 10.2 lbs.; 250 gm. *brain;* active. Chloroform for one hour (from 9:45 to 10:45 a. m.).

Dec. 4: Wt., 10.13 lbs. Casein diet.

Dec. 5: Wt., 9.9. lbs. Casein diet. *Piece of liver removed at 3:30.* No fat; no necrosis; lobule centers stain lightly; cytoplasm is somewhat granular, etc.

Dec. 6: Wt., 9.9 lbs. Experiment discontinued; mixed food.

EXPERIMENT 13.—*Brain Diet.*—Dog 19-88, a female coach puppy.

Dec. 23: Wt., 5.75 lbs. Isolated; mean-tempered; no food for twenty-four hours; in fair condition; brain *ad lib.;* does not eat very much.

Dec. 24: Wt., 5.63 lbs.; Dec. 25-27, brain *ad lib.;* eats about 150 gm. daily.

Dec. 28: Wt., 5 lbs. *Chloroform for one hour* (from 10:55 to 11:55 a. m.).

Dec. 29: Wt., 5.06 lbs. Active; meat diet.

Dec. 30: Wt., 5 lbs. Active; meat diet. *Piece of liver removed at 2:15.* Sections show *no fat;* very *little central necrosis.* The central two thirds of each lobule takes a light stain, is granular, slightly vacuolated, etc.; a few focal necroses.

Dec. 31: Developing distemper; experiment discontinued.

Jan. 5: Found dead; distemper pneumonia.

EXPERIMENT 14.—*Kidney Diet.*—Dog 19-43, a black, mongrel, female pup.

Oct. 3: Wt., 5.7 lbs. Isolated for feeding; about 10 weeks old; pup has mange and many fleas, but is active and very noisy; gave 100 gm. of *ground kidney.*

Oct. 4: Wt., 5.3 lbs.; 130 gm. *kidney;* Oct. 5, Wt., 5.25 lbs.; 140 gm. *kidney.*

Oct. 6: Wt., 5.2 lbs.; 150 gm. *kidney.*

Oct. 7: Wt., 5.13 lbs.; 150 gm. *kidney. Chloroform for one hour* (from 11:20 to 12:20).

Oct. 8: Wt., 5 lbs.; 100 gm. *kidney;* apparently not sick.

Oct. 9 Wt., 5 lbs.; 150 gm. *kidney.* Piece of liver removed in p. m.; frozen sections show practically no liver injury. Experiment discontinued.

EXPERIMENT 15.—*Liver Diet.*—Pup 5 d, a black spaniel, female.

June 3: Isolated; starvation; pup is 6 weeks old; healthy and active.

June 5: Wt., 5.7 lbs. Feeding begun; *ground liver ad lib.*

June 6. Wt., 5.63 lbs.; June 7, Wt., 5.44 lbs.; *liver ad lib.;* eats fairly well.

June 8: Wt., 5.56 lbs. *Chloroform for one hour* (from 9:15 to 10:15 a. m.).

June 9: Wt., 5.5 lbs. Remains well and active; *liver diet* continued.

June 10: Wt., 5.4 lbs. Sacrificed in a. m.; blood urea, 48 mg.; urea N., 22.5 mg.; fibrin, 275 mg. per 100 c.c. plasma.

Necropsy Report.—Liver weight, 96 gm.; no necrosis apparent; fat quite extensive—over about three fourths of each lobule.

Microscopic Report.—Liver: three fourths fatty, quite intense in central one third; no necrosis.

EXPERIMENT 16.—*Liver Diet.*—Pup 3 f, a black and white female mongrel.

May 14: Isolated; starvation; bright and active.

May 15: Wt., 5.56 lbs. Feeding begun; *ground liver ad lib.*

May 16: Wt., 5.5 lbs.; May 17, Wt., 5.11 lbs. *Liver* eaten well.

May 18: Wt., 5.5 lbs. *Chloroform for one hour* (from 10:30 to 11:30 a. m.).

May 19: Wt., 5.4 lbs. Eats very little.
May 20: Wt., 4.9 lbs. Sacrificed in p. m.; blood urea, 104 mg.; urea N., 48 mg.; fibrin, 800 mg. per 100 c.c. plasma.

Necropsy Report.—Blood definitely anemic. *Liver:* Wt., 110 gm.; tissue is not uniform; some portions are grayer than others; lobule centers are rather prominent; fat probably present. *Kidneys* show numerous subcapsular petechiae; cortices pale. *Stomach* contains pieces of excelsior.

Microscopic Report.—Liver: Slight amount of diffuse fat in neighborhood of central veins; no central necrosis; a few small lymphocytic cell nests. *Kidneys:* Quite severe hyaline necrosis in convoluted tubules; some casts yellow in color; much cell infiltration, more diffuse than in the pyelonephritis of the other pups.

Experiments 10 to 13 illustrate a decided resistance to injury afforded by feeding brain previous to chloroform anesthesia. This result was a decided surprise to us. The work of Hunt on acetonitril, using mice as experimental animals, and the work of Opie on chloroform and other drugs, using rats as experimental animals, seemed to place brain in the same class as fats, presumably on account of its lipoidal content (lecithin, cholesterol, etc.). It would appear from these experiments, however, that brain feeding does not predispose to chloroform injury in dogs.

Experiments 14, 15 and 16 demonstrate a protective value for the parenchymatous organs, liver and kidney. Such an action by these foods was also noted by Hunt, against the effects of acetonitril. Our observations on rats seem to indicate that liver diet is less uniformly protective for them than it is for dogs.

TABLE 3.—Feeding of Skeletal Muscle, Beef Heart and Beef Extract

Experiment	Diet	Chloroform	Liver Injury		Remarks
			Central Necrosis	Fat	
17 (Pup 3d)	Skeletal muscle	1 hr.	1/5	2/3; heavy zone about necrosis	Blood urea high
18 (Pup 4f)	Skeletal muscle	1 hr.	Trace	4/5; scattered	Fibrin high
19 (Pup 5e)	Skeletal muscle	1 hr.	1/2-3/5	Heavy to periphery	
20 (Pup 5b)	Beef heart	1 hr.	1/2	1/2; heavy zone about necrosis	Fibrin low
21 (Pup 19-58)	5 gm. beef extract daily for 4 days	1 hr.	Trace	1/2; heavy	Severe cytoplasmic injury without definite necrosis
22 (Adult 19-61)	10 gm. beef extract daily for 5 days	1¼ hr.	1/2-2/5	1/2; scattered	Cytoplastic injury up to 1/2

Experiment 18.—*Lean Meat Diet.*—Pup 4 f, black female mongrel.
May 23: Isolated; starvation; pup is 2 or 3 months old; bright and active.
May 24: Wt., 3.38 lbs. Feeding begun; *ground skeletal muscle ad lib.*
May 25: Wt., 3.5 lbs.; May 26, Wt. 3.3 lbs.; eats well; *meat ad lib.*
May 27: Wt., 3.38 lbs. *Chloroform for one hour* (from 9:40 to 10:40 a. m.).
May 28: Wt., 3.25 lbs. Continues active; appetite good.

May 29: Wt., 3.25 lbs. Sacrificed in a. m.; blood urea, 39 mg.; urea N., 18 mg.; fibrin, 554 mg. per 100 c.c. plasma.

Necropsy Report.—Blood clots very well. *Liver:* Wt., 56 gm. No central congestion; fat, if present, must be in small amount and diffuse; other organs negative.

Microscopic Report.—Liver: A few necrotic cells; cloudy swelling; fat over most of tissue, considerable in amount, but very finely divided. *Kidneys:* Somewhat diffuse, chronic pyelonephritis.

EXPERIMENT 19.—*Lean Meat Diet.*—Pup 5 e, a black spaniel, male.

June 3: Isolated; starvation; pup is 6 weeks old; healthy and active
June 5: Wt., 4.38 lbs. Feeding begun; *ground skeletal muscle ad lib.*
June 6: Wt., 4.25 lbs.; June 7, Wt., 4.2 lbs.; *meat ad lib.;* eats well.
June 8: Wt., 4.2 lbs. *Chloroform for one hour* (from 9:15 to 10:15 a. m.); *meat diet.*
June 9: Wt., 4.13 lbs. Contniues lively; *meat diet.*
June 10: Wt., 4.13 lbs. Sacrificed in a. m.; blood urea, 48 mg.; urea N., 22.5 mg.; fibrin, 145 mg. per 100 c.c. plasma.

Necropsy Report.—Liver: Weight, 77 gm.; central areas are red and typical of necrosis; lobules opaque almost to peripheries; other organs negative.

Microscopic Report.—Liver: Necrosis of one half to three fifths, surrounded by intense zone of fat to periphery in each lobule.

EXPERIMENT 20.—*Beef Heart Diet.*—Pup 5 b, a brown spaniel, male.

June 3: Isolated; starvation; pup is 6 weeks old; healthy and active.
June 5: Wt., 6.06 lbs. Feeding begun; *ground beef heart ad lib.*
June 6: Wt., 6.06 lbs.; June 7, Wt., 5.15 lbs.; *beef heart ad lib.;* eats fairly well.
June 8: Wt., 5.88 lbs. *Chloroform for one hour* (from 9:15 to 10:15 a. m.).
June 9: Wt., 5.8 lbs. Apparently in good condition.
June 10: Wt., 5.63 lbs. Sacrificed in a. m.; blood urea, 41 mg.; urea N., 19 mg.; fibrin, 70 mg. per 100 c.c. plasma.

Necropsy Report.—Liver: Weight, 120 gm.; lobule centers very red and distinct; opaque with fat almost to peripheries; other organs negative.

Microscopic Report.—Liver: about one half frank necrosis, surrounded by a zone of intense fat, and slight diffuse fat in the remainder. *Kidneys:* slight cloudy swelling.

EXPERIMENT 21.—*Beef Extract Diet.*—Dog 19-56, a female collie pup.

Oct. 12: Wt., 7.56 lbs. Isolated for feeding; pup is probably 2 or 3 months old; lean and active; 5 gm. *beef extract* + salt and kaolin in 150 c.c. water, by stomach tube.
Oct. 13: Wt., 7.13 lbs.; Oct. 14, Wt., 7.0 lbs.; 5 gm. *beef extract* daily.
Oct. 15: Wt., 6.7 lbs.; 4 gm. beef extract.
Oct. 16: Wt., 6.63 lbs. *Chloroform for one hour* (from 10:30 to 11:30 a. m.); 150 gm. kidney in p. m.
Oct. 17: Wt., 6.75 lbs. A little dull; 150 gm. kidney.
Oct. 18: Wt., 6.8 lbs.; 150 gm. kidney.

Piece of liver removed at 3 o'clock. Almost died under anesthetic. Sections show very little frank necrosis, but a rather severe cytoplasmic injury—large vacuolated liver cells, with heavy deposits of fat over one half of each lobule; wandering cells present.

Regenerated on kidney diet.

EXPERIMENT 22.—*Beef Extract Diet.*—Dog 19-61, a black spaniel, female adult.

Nov. 5 Wt., 23.13 lbs. Isolated before daily feeding; active and in good condition; 10 gm. *beef extract* + kaolin in 100 c.c. water by stomach tube.

Nov. 6 Wt., 22.7 lbs.; Nov. 7, Wt. 22.25 lbs.; Nov. 8, Wt., 21.75 lbs.; 10 gm. *beef extract* daily.

Nov. 9 Wt., 21.56 lbs.; 10 gm. *beef extract. Chloroform for one and one fourth hours* (from 9.45 to 11 a. m.).

Nov. 10: Wt., 21.06 lbs.; sore eye, and sneezes (distemper?); casein diet.

Nov. 11 Wt., 20.9 lbs. Casein diet; vomited; operation at 3 o'clock; *died* under anesthetic.

Necropsy Report: Organs all congested; subendocardial hemorrhages. *Liver:* Marked dimpling and probable necrosis; fat not apparent. *Kidneys:* Cortices somewhat swollen and opaque.

Microscopic Report.—Liver: Necrosis one third to two fifths; engorgement; pigmentation; fat one third, scattered. *Spleen* contains pigment.

Experiments 17 to 19 are illustrative of effects obtained from feeding lean meat to dogs previous to chloroform anesthesia. The three experiments are in themselves somewhat discordant, but an average is suggestive of a certain degree of liver protection. At least, the injury obtained is far less than that usually resulting after fat feeding and chloroform. It appears, however, that the protective action of meat feeding is inferior to that of carbohydrate feeding. Experiment 9, in Table 1, should be compared with the experiments on meat feeding alone. It will be noted that the addition of fat to meat intensifies the action of chloroform on the liver in an average case. It will be observed that these cases conform to Opie's conclusions regarding the chloroform injury in rats after meat feeding. It will be recalled that Opie found a more intense phosphorus injury after meat feeding than after fat feeding; and Salant and Swanson found that cats were rendered susceptible to injury from sodium tartrate after a meat diet.

Beef heart is tabulated with lean meat because its dietary action is more like that of muscular tissue than that of the parenchymatous organs. Experiments 21 and 22 show a rather interesting protection afforded by a diet of beef extract. This protection is entirely out of proportion to the very small amount of food concerned. For instance, Experiment 22 shows a moderate injury, but this is in an adult dog, and if starved five days and given an hour and a quarter chloroform anesthesia, he might be expected to show approximately twice the necrosis actually found.

EXPERIMENT 23.—*Thyroid Feeding Previous to Chloroform.*—Dog 18-124, a young black and white female.

Aug. 19: Wt., 14.7 lbs. Isolated; rather lean; gave 3 gm. *thyroid* powder in 200 c.c. water in a. m.; vomited; brought up two round worms; salivated. P. M.: Gave 3 gm. more *thyroid;* partly retained; left ½ gm. *thyroid* in a little damp cracker meal in cage; gave 10 drops oil of chenopodium in alcohol.

Aug. 20: Wt., 13.9 lbs. Small amount of feces and many worms in cage; bright and active; 3 gm. *thyroid* retained; ½ gm. left in cage yesterday was eaten later.

Aug. 21: Wt., 12.94 lbs.; 3 gm. *thyroid* retained.

Aug. 22: Wt., 12.63 lbs.; 3 gm. *thyroid* in a. m. Chloroform for one and one-fourth hours (from 2:25 to 3:40 p. m.).

Aug. 23: Wt., 13.0 lbs. Active; diet of sugar and potatoes.

Aug. 24: Wt., 12.5 lbs. Bright and active: left potatoes in cage. *Piece of liver removed* at 10:30 a. m. Sections show two fifths to one half necrosis, and slight surrounding cell injury, very little fat.

Regenerated on carbohydrate diet.

TABLE 4.—THYROID FEEDING

Experiment	Diet	Chloroform	Liver Injury		Remarks
			Central Necrosis	Fat	
23 (Adult 18-124)	3 gm. powdered thyroid daily, 4 days	1¼ hr.	2/5-1/2	Trace	Cells somewhat vacuolated beyond actual necrosis
	Starvation 4 days (control)	1¼ hr.	1/2	1/3: moderate	Cells somewhat vacuolated beyond actual necrosis
24 (Pup 19-43)	Thyroid and sugar	1 hr.	0	0	Nests of cells suggesting beginning abscesses
25 (Pup 19-47)	Thyroid and cottonseed oil	1 hr.	3/5-2/3	Light; in necrosis	
26 (Pup 19-47)	Thyroid and kidney	1 hr.	0	Trace	

EXPERIMENT 23.—*Fasting Control.*—Dog 18-124 (continued).

Oct. 11: Wt., 13.75 lbs. Isolated for *starvation* before daily feeding; active.

Oct. 12: Wt., 13.44 lbs.; Oct. 13, Wt., 12.25 lbs.; *fasting.*

Oct. 14: Wt., 13 lbs. In good condition; fourth day of fasting. *Chloroform for one and one fourth hours* (from 2 to 3:15 p. m.).

Oct. 15: Wt., 12.44 lbs. Bright and active; fat diet.

Oct. 16: Wt., 12.38 lbs. Fat diet.

Piece of liver removed at 3:30 p. m. Sections show one half necrosis; fat over one third, moderate; some vacuolated, injured cells surrounding necrosis.

Regeneration on fat diet.

EXPERIMENT 24.—*Thyroid + Sugar Diet.*—Dog 19-43, a black mongrel female pup.

Oct. 22: Wt., 5.25 lbs. Isolated for feeding; mange is very bad, but pup is extremely active; previously on kidney diet; operative wound healed. *Diet* consists of 10 gm. glucose, 50 gm. cane sugar, 1 gm. thyroid powder, and kaolin in 100 c.c. water by stomach tube.

Oct. 23: Wt., 4.9 lbs; Oct. 24, Wt, 4.75 lbs.; *sugar* and *thyroid* as before. Oct. 25: Wt., 4.63 lbs. *Cane sugar* increased to 60 gm.; other constituents as before.

Oct. 26: Wt., 4.44 lbs. Very skinny; mange getting worse; diet same as yesterday. *Chloroform for one hour* (from 3:30 to 4:30 p. m.).

Oct. 27: Wt., 4.3 lbs. Somewhat dull; beef extract by stomach tube.

Oct. 28: Found dead.

Necropsy Report.—Skin shows extensive mange; fat is atrophied throughout; *liver* is somewhat engorged; no necrosis apparent; perhaps a trace of fat; *left lung shows* atelectasis and hypostasis laterally in lower lobe; other organs negative.

Microscopic Report.—Lungs: Atelectasis; edema; a few round cells and multinuclears. *Liver:* no fat; no central necrosis; cell nests of focal necrosis. *Kidneys:* focal necroses.

EXPERIMENT 25.—*Thyroid and Cottonseed Oil Diet.*—Dog 19-47, a black mongrel female pup.

Oct. 22: Wt., 5.2 lbs. Isolated for feeding; quite active; previously on kidney-thyroid diet; wound is healed; 35 c.c. *cottonseed oil,* 1 gm. *thyroid* powder, and 40 c.c. water mixed and given by stomach tube.

Oct. 23: Wt., 4.94 lbs.; Oct. 24, Wt., 4.88 lbs.; oil and thyroid as before.

Oct. 25: Wt., 4.8 lbs. Oil increased to 40 c.c.; 1 gm. thyroid as before.

Oct. 26: Wt., 4.63 lbs. Oil and thyroid as yesterday. *Choloroform for one hour* (from 3:30 to 4:30 p. m.).

Oct. 27: Wt., 4.8 lbs. Active: mixed food; gelatin.

Oct. 28: Wt., 4.7 lbs. Active; gelatin by stomach tube. *Piece of liver removed* at 2:30 p. m. Necrosis three fifths to two thirds; fat +.

Oct. 29: Wt., 4.44 lbs. Dull: mange bad; gelatin diet.

Oct. 30: Found dead.

Necropsy Report.—Mange very bad; emaciated; *thymus* and *mediastinal lymph nodes* quite red; *liver* still shows severe injury—necrosis and fat; other organs negative.

Microscopic Report.—Liver: much cell debris removed; one third to two fifths unrepaired; a little fat in lobule centers. *Kidneys:* pyelonephritis.

EXPERIMENT 26.—*Thyroid and Kidney Diet.*—Dog 19-47, a black mongrel female pup.

Oct. 4: Wt., 5.9 lbs. Isolated for feeding; pup is 10 weeks old; has mange and many fleas; very active and noisy; 130 gm. ground *kidney* and 1 gm. *thyroid* powder.

Oct. 5: Wt., 5.75 lbs.; 140 gm. *kidney* and 1 gm. *thyroid.*

Oct. 6: Wt., 5.7 lbs.; 150 gm. *kidney* and 1 gm. *thyroid.*

Oct. 7: Wt., 5.7 lbs.; 150 gm. *kidney* and 1 gm. *thyroid.*

Oct. 8: Wt., 5.63 lbs.; 50 gm. *kidney* and 1 gm. *thyroid. Choloroform for one hour* (from 9:30 to 10:30 a. m.).

Oct. 9: Wt., 5.44 lbs.; 150 gm. *kidney* and 1 gm. *thyroid;* clinically all right.

Oct. 10: Wt., 5.38 lbs.; 150 gm. *kidney* and 1 gm. *thyroid. Piece of liver removed* at 3 p. m. Sections show *no necrosis; trace of fat.*

Hunt's observations on the protective action of thyroid against acetonitril poisoning suggested the use of thyroid in some of our experiments. The effect of large doses of thyroid in increasing oxidation and protein break down is well recognized.

Schryver[21] and, later, Morse[22] have studied the autolysis in vitro of livers from thyroid-fed animals. Whipple and Christman[23] have shown that thyroid insufficiency causes no change in the liver function as measured by phenoltetrachlorphthalein. Burge[24] has found that thyroid feeding increases the catalase content of blood, and decreases it in the heart, and probably in fat, and skeletal muscles. He has suggested that the increased rate of oxidation may be due to the increased catalase in the blood, while decreased catalase in heart, skeletal muscles and fat may account for increased autolysis in these tissues, for, since oxidation is low, less autolyzing enzymes are destroyed, and autolysis increases.

---

21. Schryver, S. B.: J. Physiol. **32**:159, 1905.
22. Morse, M.: J. Biol. Chem. **22**:125, 1915.
23. Whipple, G. H., and Christman, P. W.: J. Exper. M. **20**:297, 1914.
24. Burge, W. E., Kennedy, J., and Neill, A. J.: Am. J. Physiol. **43**:433, 1917.

Kuriyama[25] has reported that in thyroid-fed rats the storage of glycogen does not occur readily, even on very high carbohydrate intake. Also, glycogen disappears rapidly on feeding thyroid under normal conditions. The diastase content of blood and liver remains about normal; the disappearance is probably accounted for by increased metabolism.

The experiments in Table 4 indicate that thyroid feeding has no influence on liver injury following chloroform anesthesia. The thyroid powder employed was a commercial preparation (Armour's). This preparation had been tested in metabolism experiments, and it was shown that the amounts given would increase the fasting level of nitrogen urinary excretion at least 50 per cent. above normal. Experiment 23 shows practically an identical amount of necrosis after thyroid feeding, and after simple starvation. The pups which were given 1 gm. of thyroid daily in addition to their regular food showed the amount of necrosis which we expect following the same diets without thyroid. The only unusual point about the series is that very little fat was found in the injured livers. This may have been due to an increased oxidation; or it may be coincidence in this particular series. An animal fed 3 gm. thyroid daily for four days, followed by hydrazin sulphate subcutaneously, showed the typical fatty liver of hydrazin poisoning. It may be worth mentioning that two rats fed fat plus thyroid, then chloroformed, died a day sooner than the controls receiving fat alone.

TABLE 5.—DIETS OF SKIM MILK; CASEIN AND GELATIN

Experiment	Diet	Chloroform	Liver Injury		Remarks
			Central Necrosis	Fat	
27 (Pup 3a)	Skim milk	1 hr.	0	1/2; slight, diffuse	Glycogen +
28 (Pup 19-46)	Casein and cracker meal	1 hr.	0	Trace	
29 (Pup 19-46)	Casein	1 hr.	0	0	
30 (Adult 19-01)	Casein	1¼ hr.	0	0	Slight congestion
31 (Pup 4a)	Gelatin	1 hr.	2/5	Narrow zone around necrosis	Fibrin low
32 (Pup 5a)	Gelatin and sugar	1 hr.	Trace	1/2; moderate	Glycogen +
33 (Pup 19-45)	Alfalfa meal and crackermeal	1 hr.	1/2-3/5	Heavy to periphery	Did not seem to eat very much, but maintained weight very well

EXPERIMENT 27.—*Skim Milk Diet.*—Pup 3 a, a black female mongrel.
May 14: Isolated; starvation; apparently in good health; active and lean.
May 15: Wt., 5.06 lbs. Feeding begun; *skim milk ad lib.*

25. Kuriyama, S.: J. Biol. Chem. **33**:193, 1918.

May 16: Wt., 5.06 lbs.; May 17, Wt., 5.4 lbs.; *milk* as before.

May 18: Wt., 5.25 lbs. *Milk* early in morning. *Choloroform for one hour* (from 10:30 to 11:30 a. m.).

May 19: Wt., 4.56 lbs. Seemed to lose appetite temporarily, but continues lively; *milk* continued.

May 20: Wt., 5.0 lbs. Sacrifice in a. m.; blood urea 32 mg.; urea N., 15 mg.; fibrin, 310 mg. per 100 c.c. plasma.

Necropsy Report.—Liver: weight, 88 gm.; central veins are, perhaps, slightly more prominent than normal; *kidneys* contain many small cysts, 2 mm. in diameter.

Microscopic Report.—Liver: no necrosis; very slight amount of diffuse fat; considerable glycogen present, especially in peripheral zones; central areas stain darker. *Kidneys* are cystic, probably congenital.

EXPERIMENT 30.—*Casein Diet.*—Dog 19-91, a large male hound.

Dec. 23: Wt., 49.0 lbs. Isolated, after daily feeding; dog is healthy and active.

Dec. 24: Wt., 48.5 lbs. Feeding begun; 100 gm. *casein* made into mush and given by spoon.

Dec. 25-27: 100 gm. *casein* daily.

Dec. 28: Wt., 44.75 lbs. Active and bright. *Chloroform one and one fourth hours* (from 9 to 10:15 a. m.).

Dec. 29: Wt., 43.4 lbs. Not as active as usual; gelatin diet.

Dec. 30: Wt., 42.2 lbs. Quiet; gelatin diet. *Piece of liver removed* at 3 p. m. Sections show no necrosis and no fat; tissue looks normal; slight congestion.

Dec. 31: Wt., 42.06 lbs. Experiment discontinued.

EXPERIMENT 31.—*Gelatin Diet.*—Pup 4 a, a black and white female mongrel.

May 23: Isolated; starvation; pup is probably about 4 months old; still has puppy teeth, but fur is replaced by coarse hair of adult.

May 24: Wt., 6.44 lbs. Feeding begun; 25 gm. *gelatin* + salt and kaolin, dissolved and divided into two daily feedings by stomach tube.

May 25: Wt., 6.3 lbs.; May 26, Wt., 6.3 lbs.; *gelatin* as before; very lively.

May 27: Wt., 6.0 lbs. *Choloroform for one hour* (from 10:50 to 11:50 a. m.).

May 28: Wt., 5.88 lbs. Continues very active.

May 29: Wt., 5.75 lbs. Sacrificed in a. m.; blood urea, 29 mg.; urea N., 13.4 mg.; fibrin, 80 mg. per 100 c.c. plasma.

Necropsy Report.—Clots flabby. *Liver:* weight, 91 gm. Lobule centers large and red, representing probably one third or more necrosis, surrounded by an opaque area of fat; peripheries translucent and normal; remaining viscera normal in gross.

Microscopic Report.—Liver: about two fifths central necrosis, with congestion and some collapse; a little fat at edge of necrosis, extending into the latter, and out in the less affected tissue. Spleen is hyperemic; giant cells numerous.

EXPERIMENT 32.—*Gelatin and Carbohydrate Diet.*—Pup 5 a, a collie, male.

June 3: Isolated; starvation; pup is about 2 months old; bright and active.

June 5: Wt., 6.25 lbs. Feeding begun; mixture given by stomach tube consisted of 25 gm. gelatin and 25 gm. cane sugar daily; rice and potatoes left in cage, but not touched.

June 6: Wt., 6.06 lbs. *Gelatin* and *sugar* as before.

June 7: Wt., 6 lbs. *Sugar* increased to 35 gm.; *gelatin* still 25 gm.

June 8: Wt., 6 lbs. *Chloroform for one hour* (from 10:25 to 11:25 a. m.); food as yesterday.

June 9: Wt., 5.94 lbs. Lively; mixture by stomach tube as before.

June 10: Wt., 5.94 lbs. Sacrificed in a. m.; blood urea, 48 mg.; urea N., 23 mg.; fibrin, 135 mg. in 100 c.c. plasma.

Necropsy Report.—Liver: weight, 156 gm.; necrosis not apparent in gross; central one half to three fifths of lobules look yellow and opaque; no gross lesions in other organs.

Microscopic Report.—Liver: Occasional necrotic cells; moderate amount of fat in central half of lobules; large deposits of glycogen in peripheral two thirds.

EXPERIMENT 33.—*Alfalfa Meal Plus Cracker Meal Diet.*—Dog 19-45, a black mongrel female pup.

Oct. 4: Wt., 9.13 lbs. Isolated for feeding; pup is 10 weeks old; has mange; very active and noisy; 100 gm. *alfalfa meal* + 50 gm. *cracker meal;* mixture cooked; ate one third.

Oct. 5: Wt., 8.94 lbs. Mixture *alfalfa meal* and *cracker meal* half and half.

Oct. 6: Wt., 8.94 lbs. Mixture as yesterday, moistened with juice of boiled liver.

Oct. 7: Wt., 8.94 lbs.; 100 gm. *alfalfa meal* + 100 gm. *cracker meal* boiled; eats a little.

Oct. 8: Wt., 8.7 lbs. Mixture *ad lib.;* does not eat very much. *Chloroform for one hour* (from 9:30 to 10:30 a. m.).

Oct. 9: Wt., 8.38 lbs. Liver diet; active; does not appear sick.

Oct. 10: Wt., 8.5 lbs.; liver diet. *Piece of liver removed* at 1:45. Sections show one half to three fifths necrosis and heavy deposits of fat to periphery. Regeneration on liver diet.

Skim milk seems to be a diet quite protective against chloroform injury. Considering the results obtained from casein feeding, also presented in Table 5, it is obvious that skim milk contains two protective substances: sugar and casein; the only difficulty in attaining protection is the necessary consumption of large quantities of fluid, and this is possible with pups, at least. The protection afforded dogs by a casein diet seems to be very complete, since even the large, active adult dog, 19-91, showed no subsequent injury. A small series of rats showed a slight, irregular protection to chloroform injury following a diet of cottage cheese.

The one experiment in feeding gelatin alone suggests an inefficient protection; Experiment 32 indicates that the lack of protection from gelatin (unlike that of fat) does not detract from the protective action of sugar feeding. Whether the difference here noted between casein and gelatin is associated with their relative ability to yield sugar in the body metabolism, or with some other factor, it is difficult to say.

No doubt Experiment 33 may be interpreted to mean that, although the pup ate enough of the bulky mush to maintain weight, enough of the carbohydrate, cracker meal, was not ingested to afford protection; and that the alfalfa meal was not of equal value in the rôle of protective food. From the amount of injury, it may be argued that the mixture was actually harmful, but it seems more likely that the alfalfa meal acted simply as roughage and not as food in the dog's digestive economy.

TABLE 6.—Sugar and Fat Intravenously During Anesthesia; Amino-Acids Shortly Before Anesthesia

Experiment	Diet	Chloroform	Liver Injury		Remarks
			Central Necrosis	Fat	
34 (Adult 19-28)	Starvation 4 days (control)	1¼ hr.	2/5	Moderate throughout	
	Starvation 4 days. 15-20 gm. casein digest 15 min. before chloroform	1¼ hr.	2/5	Moderate throughout	
35 (Adult 18-135)	Starvation 3 days. 200 c.c. cream intravenously during chloroform	1¼ hr.	3/5	Heavy to periphery	Septicemia; died from combination of injuries
36 (Adult 18-56)	Starvation 3 days. 400 c.c. 10% glucose intravenously during chloroform	1½ hr.	4/5	Moderate throughout	Fatal injury

Experiment 34.—*Starvation (Control).*—Dog 19-28, a fox terrier, male adult.

Nov. 29: Wt., 19 lbs. Isolated for starvation; quiet; very fat.

Nov. 30: Wt., 18.2 lbs.

Dec. 1: In good condition.

Dec. 2: Wt., 17.63 lbs.; still fat. *Chloroform for one and a quarter hours* (from 9:45 to 11 a. m.).

Dec. 3: Wt., 17.25 lbs. Gave gelatin; vomited; not sick in appearance.

Dec. 4: Wt., 16.7 lbs. Gave gelatin; vomited. *Piece of liver removed* at 4 p. m. About three fifths necrosis; fat + +.

Dec. 5: Wt., 16.13 lbs. Wound bleeds somewhat; vomits gelatin; feeding experiment discontinued.

Experiment 34.—*Starvation; Amino-Acids Just Before Chloroform.*—Dog 19-29 (continued); fox terrier, male adult.

Dec. 18: Wt., 17.25 lbs. Isolated for starvation; bright and in good condition, except that abdominal wound has a slight superficial sinus.

Dec. 19 to 20: No food.

Dec. 21: Wt., 15.8 lbs. Bright and healthy. *Chloroform for one and a quarter hours* (from 11:15 to 12:30). Gave between 15 and 20 gm. *casein digest* by stomach tube a few minutes before anesthesis; digest contains 63.7 mg. amino-nitrogen per gram. Lean meat *ad lib.* in p. m.

Dec. 22: Wt., 16.2 lbs. Meat diet; eats well; not sick clinically.

Dec. 23: Wt., 16 lbs. Meat *ad lib.* Piece of liver removed at 2:30 p. m. Sections show two fifths necrosis; fat + +. Regenerated on lean meat.

Experiment 35.—*Cream Intravenously at Time of Anesthesia.*—Dog 18-135, a long-haired, black male (old dog).

June 15: Wt., 55.6 lbs. Isolated (after daily feeding); starvation; water *ad lib.;* dog is bright and active.

June 16 to 17: Fasting.

June 18: Wt., 51.5 lbs. *Chloroform for one and a half hours* (from 2:50 to 4:20 p. m.). Gave intravenously during anesthesia 200 c.c. of *cream* from the top of a quart of milk, mixed with 200 c.c. of physiologic sodium chlorid solution.

June 19: Wt., 52.4 lbs. Quite sick; very thirsty; gave the dog liver to eat.

June 20: Wt., 51.1 lbs. Better clinically; ate liver well. *Piece of liver* removed at 1:30 p. m.

June 21: Found dead.

Necropsy Report.—Evidence of septicemia (from nonpasteurized cream). *Heart:* Blood partially clotted (body still warm). Subepicardial and subendocardial hemorrhages; two subendocardial infarcts in left ventricle; small myocardial abscesses; old thickening and apparent shrinkage of mitral flaps. *Lungs:* Right lung shows a thrombus in middle lobe; left is atelectatic in lateral border of lower lobe.

Liver: weight, 799 gm.; very friable; red dots of central necrosis, and fat deposits to lobule periphery; frequent opaque, white spots of various sizes suggest abscesses. *Spleen:* fibrous; no pulp reaction noticeable. Kidneys: capsule strips with slight resistance leaving a rough surface; abscesses visible on surface; cortices swollen, markings blurred, opaque patches and streaks (evidently acute nephritis).

Microscopic Report.—Heart: endocarditis and myocarditis. *Lungs:* hemorrhages and some consolidation; fat in vessel walls, thrombi, and in interalveolar tissue. *Liver:* about three fifths necrosis; practically all of remainder is fatty; much brown pigment. *Pancreas* congested. *Kidneys:* severe nephritis, especially of tubules; interstitial edema; abscess formation; casts, etc.; diffuse fat in epithelium of collecting tubules, and in blood vessels (apparently thrombosed).

EXPERIMENT 36.—*Glucose Intravenously at Time of Anesthesia.*—Dog 18-56, a brindle and white bull, female.

June 10: Wt., 20.8 lbs Isolated; starvation; in good condition; extremely active; Water *ad lib.*

June 13: Wt., 18.4 lbs. Chloroform for one and a half hours (from 3:10 to 4:40 p. m.); 10 per cent. solution of glucose given continuously during anesthesia; 460 c.c. in all.

June 14: Wt., 17.63 lbs. Quieter than usual; thirsty.

June 15: Wt., 18.06 lbs. Appears dull. *Piece of liver removed* at 9:30 a. m.

June 16: Found dead.

Necropsy Report.—Slight amount of free blood in peritoneal cavity, evidently due to deficiency in clotting at point of operation in liver. Blood in heart is partially clotted; clots flabby, like soft jelly. Spots on posterior surface of lungs look suspicious of hemorrhage. *Liver:* weight 267 gm.; appears to have about one half necrosis, surrounded by a zone of fat, and a narrow rim of normal tissue. *Spleen* has knobby projections, evidently of hemorrhage; other viscera negative.

Microscopic Report.—Liver: necrosis of four fifths; fatty throughout. There seems to have been a slight removal of necrotic cell debris between operation and death.

Glucose or cream intravenously during anesthesia seems to have little effect on the liver injury resulting from chloroform. It is even possible that the glucose solution (Experiment 36) may have had a deleterious effect, since the necrosis is so extreme. It will be noted that the necrosis in the case in which cream was injected is less intense than in the case in which sugar was introduced. Positions are reversed when these substances are fed in the days previous to chloroform

anesthesia. No doubt it will be suggested by some one that the fat in the blood stream "fixed" a large percentage of the chloroform which might otherwise have injured the liver. Such may have been the case, but the liver sustained a severe injury, notwithstanding. The dog receiving cream (Experiment 35) showed septicemia, but this did not modify the liver picture appreciably, since the central necrosis occurred before the septicemia developed.

We lost two valuable dogs in the attempt to give a solution of amino-acids intravenously during the administration of chloroform anesthesia. A previous injection of some of the same material into a normal, unanesthetized animal had produced no reaction, but the combination with chloroform was fatal. To surmount this difficulty, a third dog was given casein digest in weak acid a few minutes before the anesthetic was started, with the idea that the amino-acids would be passing into the portal circulation during the period of chloroform anesthesia. The result shows a small but quite definite lessening of necrosis as compared with a simple starvation control on the same animal. We should remember that these amino-acids resulted from the digestion of casein which by itself has such a marked protective action against chloroform poisoning.

Burge[26] has shown that catalase, supposed by him to govern oxidations, is decreased very extensively in chloroform anesthesia. On the other hand, the ingestion of foodstuffs increases this enzyme. Proteins have the greatest power in this respect, the amino-acids being the stimulating principles; fats are less powerful stimulants than proteins, but more efficient than carbohydrates; the glycerin radical acts in the case of fats, and the simple sugars, principally dextrose, in the case of carbohydrates. Casein has been shown to be very efficient in causing an increase in catalase. It is understood that the increase in catalase from the ingestion of foodstuffs is more or less temporary, being most noticeable during the period of digestion. Burge has found a decrease in catalase during starvation, but has reported very little regarding the catalase level maintained by individual diets through the course of feeding experiments lasting several days.

It would seem, therefore, that a substance tending to increase the enzyme catalase in a given period would tend to neutralize the action of a concurrent chloroform anesthesia, providing, of course, that

---

26. Burge, W. E.: Science **46**:618, 1917; J. Pharm. and Exper. Therap. **12**: (Nov.) 1918; Am. J. Physiol. **47**:351, 1918. Burge, W. E., and Neill, A. J.: Am. J. Physiol. **43**:58, 1917; idem. **45**:500, 1918; idem. **46**:117, 1918; idem. **47**:13, 1918. Burge, W. E., Neill, A. J., and Ashman, R.: Am. J. Physiol. **45**:388, 1918.

chloroform produces its effect either as an anesthetic or as a protoplasmic poison, or both, by a reduction of oxidation. Such a neutralizing effect was not produced by injecting either sugar or fat; the result with casein digest is more suggestive, but far from conclusive.

GENERAL DISCUSSION

No adequate explanation is offered for the protective or injurious effect of any diet in modifying the action of chloroform. It will be recalled that Graham correlated resistance with glycogen content of the liver. This is an attractive theory, and seems to hold true in some cases. Carbohydrate diets certainly build up liver glycogen; the storage can be readily seen in ordinary hemotoxylin and eosin stained sections. However, if Kuriyama's work is reliable, glycogen storage is very difficult, and glycogen elimination is very prompt when thyroid is given; yet in our series of experiments the protective action of sugar or kidney is not changed by the addition of thyroid, and thyroid alone previous to chloroform does not modify the picture of ordinary starvation plus chloroform.

Furthermore, it is difficult to see why brain, which has practically no free carbohydrate, should be protective; and why kidney and liver should be so much more protective than skeletal muscle. It is true that liver, especially, has an appreciable carbohydrate content, but it is scarcely credible that such a small difference in percentage between liver and muscle should make a recognizable difference in liver susceptibility. The beef extract which we used contained only a trace of reducing substances (Fehling's test) and showed no more after acid hydrolysis; yet this extract in relatively small amounts built up a distinct resistance to the action of chloroform, or at least prevented the development of a susceptibility. The casein used in our feeding experiments was free from reducing sugars (Fehling's test) both before and after acid hydrolysis, yet this casein was a highly protective food. We do not mean to intimate that these proteins, and simpler nitrogenous products are not capable of yielding sugars in the process of body metabolism, and that the sugars so formed might not be stored as glycogen under certain conditions, but the evidence is not clear in every case. The preferability of certain proteins, for example, casein, or kidney proteins, over other proteins, for example, gelatin or skeletal muscle, for sugar formation is more or less conjectural. It may be that the ingested food does not form liver glycogen itself, but has a sparing action on the glycogen already stored, insofar as it is able to furnish the fuel for heat and energy. This is conjecture again;

we usually speak of carbohydrates sparing proteins, rather than the reverse. Moreover, fat, which is an excellent fuel, has no such action.

Opie's idea that ingested fat is stored, partly by the parenchymatous organs, and that the "fixing" of chloroform by this fat results in a greater injury to the cells in certain localities, will hardly explain the severe injury sustained by starved animals.

Whatever the protective action may be, it certainly seems to be built up by the body, and does not lie in the foods as such. This is indicated by the lack of protection given by glucose when injected intravenously during chloroform anesthesia.

SUMMARY

Starved animals are very susceptible to liver injury from chloroform. A maximal injury is to be expected.

Sugar, and diets rich in carbohydrates, fed in the days preceding chloroform anesthesia, exert a marked protective action against liver injury.

Fat alone, or combinations of food containing fat in large proportion, induce a maximal susceptibility to liver injury comparable to starvation.

Skeletal muscle and heart muscle seem to have a slight protective action.

Beef extract is highly protective in proportion to its actual food value.

The parenchymatous organs, liver and kidney exert a considerable amount of protection.

Brain, although rich in lipoidal substances, is a protective food against chloroform injury, thus being in marked contrast to fat mixtures.

Skim milk alone, and commercial casein alone, or in combination with cracker meal, are highly protective diets.

Gelatin has but slight protective action itself, but when given in mixtures with sugar, does not lessen the protective value of the latter.

Thyroid powder, given alone, or in combination with foods (sugar, fat, etc.) apparently does not modify the chloroform injury which is to be expected without such addition.

Glucose, or cream, given intravenously during chloroform anesthesia, do not modify the effect of the drug on a starved animal. One instance in which casein digest (high in amino-acid content) was given by stomach tube a few minutes before chloroform anesthesia, indicates a slight protective action.

No single theory so far advanced will explain this peculiar protective action of certain food substances against the liver injury of chloroform anesthesia. It certainly is a reaction of the liver cells, not of substances circulating in the blood stream.

These facts should not be lost sight of in the management of any human cases in which chloroform is indicated. The patient should be given liberal amounts of carbohydrates and milk for at least two days preceding the anesthesia. It can not be too often emphasized that it is dangerous to give chloroform to man or animal whenever a fasting period has preceded the administration of the anesthetic.

THE INFLUENCE OF DRUGS AND CHEMICAL AGENTS ON THE LIVER NECROSIS OF CHLOROFORM ANESTHESIA*

PAPER II

N. C. DAVIS AND G. H. WHIPPLE, M.D.
SAN FRANCISCO

Among the various explanations offered for the well known chloroform livery injury, the theory of Graham[1] is, perhaps, the most attractive. This author believes that in the presence of water and oxygen in the body, chloroform is split and hydrochloric acid and carbon dioxid are formed; the hydrochloric acid then kills a certain amount of liver parenchyma, either by direct action or by secondary asphyxia. We must admit that we are unable to follow the chemical reactions as outlined by Graham. Furthermore, it is just as difficult to explain chloroform necrosis as to explain why chloroform passes by all body tissues until it reaches the liver, where the hypothetical chemical reaction takes place with release of hydrochloric acid. The specific susceptibility of the liver cell for chloroform is the riddle which has so far defied solution. Graham produced liver necrosis in dogs by injecting hydrochloric acid into the portal vein; the necrosis differed from typical chloroform injury in being portal (peripheral) rather than central. Hydrochloric acid given by stomach tube to rabbits generally proved fatal; at necropsy the animals were found to have fatty livers, and hemorrhages in the stomach and duodenum. He found that the areas of central necrosis in chloroform poisoning gave an acid test with neutral red, and a chlorin test with silver nitrate and sunlight.

Graham records experiments in which sodium carbonate in hypertonic saline solution, given intravenously during chloroform anesthesia markedly inhibited the production of necrosis, although the fatty changes were comparable to the controls which received normal saline only. Furthermore, it was found that central liver necrosis followed the use of: (1) dichlor- and tetrachlor-methane (in proportion to the chlorin content); (2) tribrom- and tri-iodo-methane; (3) monochlor-, monobrom-, monoidodo-, and dibrom-ethane (in pro-

* From the George Williams Hooper Foundation for Medical Research, University of California Medical School.

1. Graham, E. A.: J. Exper. M. **22**:48, 1915; J. Biol. Chem., Proc. **20**:25, **1915**; J. A. M. A. **69**:1666, 1917; Am. J. Surg., Quart. Sup. Anesth. 1917, p. 34; Dental Summary **37**:506, 1917; J. Nat. Dent. Assn. **4**:733, 1917.

portion to the ease of formation of halogen acids). In some cases an increase of the neutral salts of the halogen acids could be demonstrated subsequently in the urine. Ether and chloral hydrate, which do not yield halogen acids, do not form necroses, but give only edema, and fat infiltration to a less degree.

We have attempted to repeat Graham's observations on the protective action of sodium carbonate given intravenously during chloroform anesthesia. He administered the anesthetic over a period of four and one-half hours. We have found that liver injury is much more uniform after a preliminary starvation; this renders the animals more susceptible to injury, hence a shorter period of anesthesia is advisable. Our usual procedure is to give one and one-half hours of chloroform anesthesia (drop method, with personal attention) to dogs which have fasted three days, and one and one-quarter hours to those which have fasted four days. Graham gave his solutions through a cannula in the saphenous vein; we have given the fluid into the external jugular vein, through a needle attached by tubing to a raised funnel. Graham used a hypertonic saline solution of sodium carbonate, 10 gm. Na_2CO_3 and 14 gm. NaCl per liter of water; we have made up similar solutions in each case. A perusal of Graham's protocols shows that to one dog he gave 33⅓ c.c. of carbonate solution per kilogram, and to the other 30 c.c. per kilogram; in our series we gave 34 c.c. per kilogram to the first dog, 30 c.c. per kilogram to the second, 33.8 c.c. per kilogram to the third, and 35+ c.c per kilogram to the fourth. Instead of sacrificing on the second day, we have removed a small piece of liver under ether anesthesia on the second day; the technic of this procedure is discussed more fully in the preceding article of this series. Tissue has been fixed with formaldehyd solution, and both hematoxylin and eosin, and fat stains made.

The following table and protocols indicate the results of our experiments. These experiments indicate that Graham's claims are based on incomplete or inaccurate observations. Carefully controlled experiments show beyond a reasonable doubt that carbonates given intravenously or by mouth have no effect whatsoever on the injurious action of chloroform on the liver. Graham gives no statements concerning the diets in his experiments and we are inclined to believe that the diet conditions must explain his observations.

EXPERIMENTAL OBSERVATIONS

It will be observed in all the tables that the amount of liver necrosis is estimated in fractions, ½, ⅔, etc. This means that inspection of the microscopic sections gave clear histological evidence of a uniform typical hyaline necrosis involving each lobule to the extent of ½ or ⅔

of all the cells of these lobules. The necrosis is invariably central and unless otherwise stated is clear cut and uniform throughout. All the evidence shows that there is great uniformity in this reaction — one group of liver lobules, therefore, gives a true picture representing all the liver lobules or the whole organ.

TABLE 7.—Intravenous Injection of Buffer Solutions During Chloroform Anesthesia

Experiment	Starvation, Days	Supplementary Treatment During Anesthesia	Chloroform, Hours	Liver Injury		Remarks
				Central Necrosis	Fat	
40 (Dog 18-82)	3	Sodium carbonate in hypertonic saline intravenously	1½	1/2 to 3/5	1/2; moderate	Previously on metabolism; sugar feeding
41 (Dog 19-5)	3	Sodium carbonate in hypertonic saline intravenously	1½	1/4 to 1/3	Scattered to periphery	Cytoplasmic injury severe up to 1/2
42 (Dog 19-6)	3	Normal saline intravenously (control)	1½	1/4 to 1/3	Trace	Cytoplasmic injury severe up to 1/2
43 (Dog 19-6)	3	Sodium carbonate in hypertonic saline intravenously	1½	1/4 to 1/3	Moderate to periphery	Cytoplasmic injury severe up to 1/2
44 (Dog 19-74)	4	Sodium carbonate in hypertonic saline intravenously	1¼	1/2 +	Trace; diffuse throughout	
	4	No injection (control)	1¼	1/2	1/3; moderate	
45 (Dog 18-131)	3	Phosphate solution intravenously	1½	3/4	1/4; heavy	Moribund at time of sacrifice on second day
46 (Dog 19-9)	3	Phosphate solution intravenously	1½	3/4 to 4/5	Light to periphery	Death shortly after operation on second day

Experiment 40.—*Carbonate Intravenously During Chloroform Anesthesia.*—Dog 18-82, a young, white, female bull.

June 8: Wt., 20.3 lbs. Isolated after daily feeding; previously on metabolism, with sugar feeding; active; somewhat skinny; one of old incisions has a superficial discharging pocket.

June 9 to 10: No food.

June 11: Wt., 18.63 lbs. *Chloroform for one and a half hours* (from 1:50 to 3:20). During the first hour of anesthesia 290 c.c. of the following solution was given intravenously: 5 gm. Na_2CO_3, and 7 gm. NaCl in 500 c.c. water. Took anesthesia poorly; recovered from effects slowly.

June 12: Wt., 18.63 lbs. Very lively.

June 13: Wt., 17.56 lbs. *Piece of liver removed at* 2 o'clock. Lost considerable blood. Gave epinephrin subcutaneously. Sections show one half to three fifths necrosis, with almost all the remaining tissue fatty. Regenerated on bread and milk.

Experiment 41.—*Carbonate Intravenously During Chloroform Anesthesia.*—Dog 19-5, an adult male airdale.

July 15: Isolated before daily feeding; starvation.

July 16: No food.

July 17: Wt., 26.75 lbs. *Chloroform for one and a half hours* (from 3:50 to 5:20). Gave intravenously during first fifty minutes of anesthesia: 3.6 gm. Na_2CO_3, and 5.4 gm. NaCl in 360 c.c. water.

July 18: Wt., 26.25 lbs. Apparently as well as usual; fat diet.

July 19: Wt., 26.13 lbs. Vomited about 2 o'clock; fat diet. *Piece of liver removed at 2:45 p. m.* Sections show a necrosis of one fourth to one third, with intense cytoplasmic injury up to one half (swollen cells without visible cytoplasm), and a scattering of fat throughout. Regenerated on fat diet.

EXPERIMENT 42.—*Saline Intravenously During Chloroform Anesthesia.*—Dog 19-6, a yellow adult male mongrel.

July 17: Wt., 30.5 lbs. Isolated after daily feeding; healthy and active.

July 18 to 19: Fasting.

July 20: Wt., 28.25 lbs. *Chloroform for one and a half hours* (from 9:15 to 10:45 a. m.); 400 c.c. M/6 NaCl intravenously during first hour of anesthesia.

July 21: Wt., 26.96 lbs. Very active. Lean meat diet.

July 22: Wt., 27.13 lbs. *Piece of liver removed at* 11 o'clock. Sections show very little fat; actual necrosis of one fourth to one third, with severe cytoplasmic reaction up to one half (cells swollen with very little cytoplasm). Regenerated on lean meat diet.

EXPERIMENT 43.—*Carbonate Intravenously During Chloroform Anesthesia.*—Dog 19-6, a yellow adult male mongrel.

Aug. 16: Wt., 30.2 lbs. Isolated after daily feeding; operative wounds healed; healthy and active.

Aug. 17 to 18: Fasting.

Aug. 19: Wt., 26.75 lbs. *Chloroform for one and a half hours* (from 9:10 to 10:40 a. m.). Gave intravenously during first hour and ten minutes of anesthesia: 4.1 gm. Na_2CO_3 and 5.74 gm. NaCl in 410 c.c. water.

Aug. 20: Wt., 25.9 lbs. Quieter than usual; fat diet.

Aug. 21: Wt., 25.2 lbs. Eats fat well; bright and active. *Piece of liver removed* at 1:15 p. m. Sections show a practically identical picture to that obtained in previous experiment with saline injection at time of chloroform. Necrosis of one fourth to one third, with severe cytoplasmic reaction up to one half (large, clear cells), fat rather heavy in central areas, and slight to periphery. (More fat than in control.) Regenerated on fat diet.

EXPERIMENT 44.—*Carbonate Intravenously During Chloroform Anesthesia.*—Dog 19-74, a young, black and white male terrier.

Nov. 18: Wt., 13.56 lbs. Isolated for *starvation* before daily feeding; recovering from distemper; rather mean-spirited; active.

Nov. 19 to 20: Starvation.

Nov. 21: Wt., 12.13 lbs. *Chloroform for one and a fourth hours* (from 8:30 to 9:45 a. m.). Gave intravenously during first forty minutes of anesthesia 1.95 gm. Na_2CO_3, and 2.8 gm. NaCl in 195 c.c. water.

Nov. 22: Wt., 11.9 lbs. Very quiet; thirsty; casein diet.

Nov. 23: Wt., 12.06 lbs. Eats nothing; vomited gelatin given by stomach tube. *Piece of liver removed* at 10:30 a. m. Sections show a strong one half necrosis; fat: trace diffuse throughout. Mixed food.

Simple Starvation and Chloroform (Control).—Dog. 19-74.

Dec. 4: Wt., 12.94 lbs. Isolated for *starvation* before daily feeding; wound from previous operation has an open spot at lower end of incision; quite active; distemper gone.

Dec. 5 to 6: Starvation.

Dec. 7: Wt., 11.8 lbs. Quite active. *Chloroform for one and a quarter hours* (from 8:30 to 9:45 a. m.); attempted to give NaCl intravenously, but could not get in veins.

Dec. 8: Appears as well as usual.

Dec. 9: Wt., 11.06 lbs. Quite active. *Piece of liver removed* at 2 o'clock; bled freely; stopped hemorrhage with a second ligature. Sections show one half necrosis; fat one third, moderate. Regenerated on beef extract.

EXPERIMENT 45.—*Phosphates Intravenously During Chloroform Anesthesia.*—Dog 18-131, a brown and white male terrier mongrel.

June 7: Wt., 25.2 lbs. Isolated after daily feeding.

June 8 to 9: No food.

June 10: Wt., 22.63 lbs. *Chloroform for one and a half hours* (from 2:50 to 4:20 p. m.); 4 gm. Na_2HPO_4 and 0.1 gm. NaH_2PO_4 in 100 c.c. normal saline were given intravenously during the first half hour of anesthesia. Muscular twitchings were observed during the first hour of anesthesia.

June 11: Dog active; apparently all right.

June 12: Wt., 19.63 lbs. Found comatose at 9 a. m.; sacrificed; blood urea, 46 mg.; urea N., 21.5 mg.

Necropsy Report.—Blood clots are flabby. *Liver* weight, 272 gm. Lobules show extensive central necrosis, with remaining tissue fatty. *Kidney* cortices look opaque; glomeruli very distinct; no hemorrhages into intestinal tract or elsewhere; two large, red, mediastinal lymph nodes were noticed.

Microscopic Report: Liver: about three fourths necrosis; remainder of tissue fatty. *Kidneys:* cloudy swelling.

EXPERIMENT 46.—*Phosphates Intravenously During Chloroform Anesthesia.*—Dog 19-9, a male collie mongrel.

Aug. 3: Wt., 32.96 lbs. Isolated before daily feeding; starvation.

Aug. 4: No food.

Aug. 5: Wt., 32.13 lbs. *Chloroform for one and a half hours* (from 1:45 to 3:15 p. m.). During one hour and ten minutes of anesthesia, gave the following intravenously: 5 gm. Na_2HPO_4, 0.5 gm. NaH_2PO_4 and 3.5 gm. NaCl in 250 c.c. water. Took the anesthetic all right but vomited a little bile stained fluid afterward.

Aug. 6: Wt., 30.9 lbs. Weak and dull; vomited sugar; retained potatoes; blood urea, 44 mg.; urea N, 21 gm.

Aug. 7: Wt., 31.25 lbs. Brighter. *Removed piece of liver* at 11 a. m; considerable hemorrhage; vomited later; died between 4 and 5 p. m.; necropsy at 5:20 p. m.

Necropsy Report.—No evidence of clotting, and blood refuses to clot on contact with tissues; peritoneal cavity full of fluid blood seeped from liver operation. *Liver:* weight, 324 gm. Central three fourths of each lobule is gorged with blood, and peripheries are opaque with fat; seepage is from needle holes in liver. *Stomach* and *intestines* contain much blood; mucosa of pyloric antrum is greatly injected—probably the site of hemorrhage.

Microscopic Report.—Liver: three fourths to four fifths necrotic; fat in dead tissue, and a little in surrounding cells. *Spleen:* engorged. *Stomach:* pseudomembrane. *Kidneys:* cloudy swelling and engorgement.

Experiment 40 shows an average amount of injury from one and one-half hours of chloroform. This dog had previously been used for an experiment, the conditions of which were slightly different. On the other occasion there had been seven days of fasting, but 100 gm. of sugar were given a few hours before chloroform anesthesia of one and one-half hours. The injury was not established, but on the fifth day after anesthesia, with sugar feeding each day, the liver was still

¼ unrepaired, with a trace of fat. We may safely conclude that no protective action is exhibited by the carbonate solution in Experiment 40.

Experiment 41 shows a relatively slight injury, but so does Control Experiment 42. These dogs were both good, healthy animals of medium weight, and received exactly the same treatment throughout, except in the solution which they received intravenously. Dog 19-6 was later used for Experiment 43, in which he received carbonate solution. The hematoxylin and eosin stained sections from the three experiments, 41, 42 and 43, might easily be passed as tissue from the same case; the control, 42, shows less fat than either of the other two.

Experiment 44 is really two experiments on the same dog. If there is any difference at all in the two injuries, there is a trace more necrosis after carbonate intravenously during anesthesia than there is when no injection was given. It may be noted that the control experiment with Dog 19-74 was performed after the carbonate experiment, while the reverse is true with Dog 19-6. This only goes to show that two successive injuries in a dog are practically the same, providing that other conditions are similar; for example, starvation period, and length of anesthesia; and that sufficient time is given between experiments to allow complete regeneration and recovery of weight, etc., to take place; the carbonate solution apparently has no influence in the matter.

In view of the supposed protective action of carbonate solution, we decided to try the action of phosphate solutions, since they, also, presumably, would have a buffer effect. Experiments 45 and 46 show the result of such trials. A little monosodium phosphate was added to the disodium phosphate in each case to reduce slightly the alkalinity of the solution, and a total amount was chosen which would certainly have some value as a buffer (from 4 to 6 gm.). From the extreme injury obtained it certainly appears that there was no protection, possibly an added insult. Greenwald[2] has recently shown that phosphate ion is not toxic, at least in its immediate action. If reference is made to paper III of this series, relative to liver regeneration on starvation and sugar feeding, it will be seen that sodium bicarbonate given by stomach tube either before or after chloroforming has no effect on the nitrogen curve or on the liver injury.

Granting that glycogen storage in the liver lessens the amount of liver necrosis, as Graham[3] has claimed, and if his dogs were not starved, another explanation may be offered for the protection observed in his experiments. Pavy and Bywaters[4] found that postmortem

2. Greenwald, I.: J. Pharm. and Exper. Therap. **11**:281, 1918.

breaking of glycogen in the liver can be stopped by an injection of 2 per cent. sodium carbonate into the living animal; Pavy and Godden[5] were able to stop chloroform or vagus stimulation glycosuria in the cat by injection of carbonate; McDanell and Underhill[6] have reported a marked reduction of epinephrin glycosuria with carbonate given intravenously in some animals. Therefore, if the animals not receiving the alkaline solution were continually losing sugar from chloroform glycosuria (quite marked in cats) over a period of four and a half hours, the liver glycogen, if it were efficacious, would perhaps be diminished enough to permit injury in Graham's experiments.

TABLE 8.—USE OF EPINEPHRIN, QUININ, STRYCHNIN AND TOXIC PROTEOSE

Experiment	Starvation, Days	Supplementary Treatment	Chloroform, Hours	Liver Injury		Remarks
				Central Necrosis	Fat	
47 (Dog 19-10)	4	Epinephrin subcutaneously on the 2 days preceding chloroform	1	1/4 to 1/3	1/3; scattered	Young, immature dog; developed abscess from injection; sacrificed. Liver necrosis surrounded by a zone of vacuolated cells; glycogen +
48 (Dog 19-4)	4	Epinephrin injection 2 days preceding chloroform	1¼	Trace	2/5; moderate	Central areas show injury (large vacuolated cells) but very little necrosis; abscess developed
49 (Dog 19-73)	4	Epinephrin subcutaneously less than 1½ hrs. before chloroform	1¼	1/2	Light; in necrosis	Abscess developed; sacrifice on second day; fat mostly in necrotic areas
50 (Dog 18-124)	4	1 gm. quinin sulph. in weak acid by stomach tube daily for 4 days	1¼	Trace	Trace	Severe cytoplasmic injury in central 1/3 or 2/5; previous exper. on same dog gave 1/2 necrosis after simple starvation (see Exper. 23)
51 (Dog 19-11)	4	Starvation only (control)	1	2/3 to 3/4	Moderate throughout	Young, immature dog; control to series 19-10, 19-11, 19-12, 19-13, distemper developed day after chloroform; found dead on second day
52 (Dog 19-13)	4	Strychnin sulph. on 2 days preceding chloroform	1	2/3 to 3/4	2/5; heavy	Piece of liver removed on second day; found dead on third day
53 (Dog 19-18)	2	Toxic proteose intravenously during chloroform	1¼	4/5	Slight to periphery	Died in less than 24 hours
54 (Dog 19-87)	0	Toxic proteose intravenously during chloroform	1¼	0	0	Dog had distemper; not on starvation, but had poor appetite; operated on second day; liver shows cloudy swelling; recovered

3. Graham, E. A.: J. Exper. M. **21**:185, 1915.
4. Pavy, F. W., and Bywaters, H. W.: J. Physiol. **41**:168, 1910-1911.
5. Pavy, F. W., and Godden, W.: J. Physiol. **43**:7, 1911-1912.
6. Underhill, F. P.: J. Biol. Chem. **25**:463, 1916. McDanell, Louise, and Underhill, F. P.: J. Biol. Chem. **29**:227, 251 and 265, 1917.

EXPERIMENT 48.—*Epinephrin Injections Previous to Chloroform Anesthesia.*—Dog 19-4, a young, female terrier.

Aug. 12: Wt., 19.3 lbs. Isolated for starvation before daily feeding; healthy and very active.

Aug. 13: Very active; 7 c.c. epinephrin (epinephrin chlorid 1:1,000) intramuscularly at 11 a. m.; 3.5 c.c. epinephrin intramuscularly at 4:30 p. m.

Aug. 14: Wt., 18.63 lbs. Weak in hind limbs. Four c.c. epinephrin subcutaneously at 9 a. m.; 7.5 c.c. epinephrin intramuscularly at 4:30 p. m.

Aug. 15: Wt., 17.63 lbs. Left hind leg extremely swollen, and cannot be used. *Chloroform for one and a quarter hours* (from 8:50 to 10:05 a. m.).

Aug. 16: Wt., 17.25 lbs. Leg much better; bright, but not active.

Aug. 17: Wt., 17.25 lbs. Abscess opening on left thigh. Piece of liver removed at 10 a. m. Sections show a mere trace of central necrosis, a few large vacuolated cells, and a scattering of small fat droplets over about two fifths of each lobule.

EXPERIMENT 49.—*Epinephrin Injection Shortly Before Chloroform Anesthesia.*—Dog 19-73, a black and tan male terrier.

Nov. 15: Wt., 17.56 lbs. Isolated before daily feeding; *starvation.* Dog is young and immature; very active.

Nov. 16: Wt., 17 lbs. Nov. 17, *starvation;* very active.

Nov. 18: Wt., 16.3 lbs. Active; in good condition; *7.5 c.c. of epinephrin* (epinephrin chlorid 1:1,000) subcutaneously at 11:45 a. m. *Chloroform for one and a quarter hours* (from 1:10 to 2:25 p. m.). At time of anesthesia the pupils were still greatly dilated, but the pulse was back to normal.

Nov. 19: Wt., 16.2 lbs. Quiet and a little dull; weak in hind limbs; beef extract diet.

Nov. 20: Wt., 15.56 lbs. Becoming toxic; vomited; sacrificed at 3:30 p. m.

Necropsy Report.—Tissue of left side of body from thigh to axilla, is necrotic in places. (Result of subcutaneous injection of epinephrin.) Viscera pale from exsanguination. *Liver:* apparently about one half fatty; necrosis does not show in gross.

Microscopic Report.—Liver: a strong one half necrotic, with fat in necrotic areas. *Spleen:* slightly congested.

EXPERIMENT 50.—*Quinin Sulphate Previous to Chloroform Anesthesia.*—Dog 18-124, a young, black and white female.

Nov. 4: Wt., 13.3 lbs. Isolated for starvation before daily feeding. Operative incisions of other operations healed. Gave 1 gm. *quinin sulphate* in weak acid by stomach tube; frothy vomitus later. (Weak acid = 50 c.c. H_2O + 8 drops conc. H_2SO_4.)

Nov. 5: Wt., 12.75 lbs.; 1 gm. *quinin sulphate* in weak acid by stomach tube; became weak and unsteady; frothy vomitus.

Nov. 6: Wt., 12.2 lbs.; 1 gm. *quinin sulphate;* reaction as before.

Nov. 7: Wt., 11.63 lbs.; 1 gm. *quinin sulphate;* reaction as before. Chloroform for one and a quarter hours (from 3:05 to 4:20 p. m.).

Nov. 8: Wt., 11.3 lbs. Quite active; mixed food.

Nov. 9: Wt., 11.9 lbs. Sacrificed at 10:30 a. m.

Necropsy Report.—Abdominal wounds are healed superficially, but show stitch abscesses in the deeper parts; mediastinal lymph nodes large and dark; viscera pale from exsanguination. *Spleen:* somewhat shrunken and firm. *Liver:* shows small stitch abscesses and extreme fibrosis at operative sutures; parenchyma shows red lobule centers—suggesting necrosis—and pale, opaque areas.

Microscopic Report.—Liver: central engorgement; practically no necrosis; severe injury (large vacuolated cells, and a trace of fat) in central one third to two fifths. *Kidney:* cells of cortex very much swollen. *Spleen:* engorged.

EXPERIMENT 51.—*Starvation (Control).*—Dog 19-11, a brown mongrel male pup.

Aug. 5: Wt., 11.8 lbs. Isolated before daily feeding; *starvation;* healthy and very active.

Aug. 6 to 7: *No food;* very active and noisy.

Aug. 8: Wt., 10.8 lbs. Healthy and active. *Chloroform for one hour* (from 12:50 to 1:50).

Aug. 9: Wt., 10.5 lbs. Quiet; developing distemper.

Aug. 10: Found dead.

Necropsy Report.—Lungs: show extensive, diffuse, bronchopneumonia, with hemorrhage, especially noticeable in lower lobes. *Liver:* weight 212 gm.; lobule centers are dark red, surrounded by a narrow zone of opaque, yellowish-white tissue. *Spleen:* shows some dark purplish patches, perhaps postmortem. *Stomach* contains a few flecks of old blood; definite hemorrhagic foci not found.

Microscopic Report.—Liver: two thirds to three quarters coagulative necrosis; heavy deposits of fat to periphery of lobules. *Kidney:* some cloudy swelling.

EXPERIMENT 52.—*Strychnin Sulphate Previous to Chloroform Anesthesia.*—Dog 19-13, a young female terrier.

Aug. 5: Wt., 14.56 lbs. Isolated before daily feeding; *starvation;* healthy and active.

Aug. 6: No food; 2.5 gm. *strychnin sulphate* subcutaneously at 12 m.

Aug. 7: Wt., 13.63 lbs. No food; 3.25 mg. *strychnin sulphate* at 5:15 p. m.

Aug. 8: Wt., 13.38 lbs. Apparently as well as usual. *Chloroform for one hour* (from 8:50 to 9:50 a. m.).

Aug. 9: Wt., 12.63 lbs. Quiet and a little dull.

Aug. 10: Wt., 12.75 lbs. Droopy. *Piece of liver removed* at 12 m.; left food in cage.

Aug. 11: Found dead.

Necropsy Report.—Body still warm; rigor mortis beginning; heart blood not clotted, but forms flabby clots slowly on contact with tissues; some free blood in peritoneal cavity, but not enough to account for death in itself; good clot over liver wound. *Liver:* weight 208 gm.; necrosis and fat very evident. *Thymus* dark, probably hemorrhagic. *Pancreas* quite dark. *Spleen* and *kidneys* normal in gross.

Microscopic Report.—Operation and necropsy show much the same picture in the *liver;* two thirds to three quarters hyaline coagulative necrosis; fine scattering of fat through necrosis, and heavy from edge to lobule periphery. *Thymus* engorged. *Kidney:* some cloudy swelling.

EXPERIMENT 53.—*Proteose Intravenously During Chloroform Anesthesia.*—Dog 19-18. Old male mongrel.

Aug. 14: Wt., 17 lbs. Isolated after daily feeding; active and healthy.

Aug. 15 to 16: Fasting.

Aug. 17: Wt., 15.7 lbs. *Chloroform for one and a quarter hours* (from 8 to 9:15 a. m.); 35 c.c. *toxic proteose solution* (mixture from three experimental obstruction dogs); 200 c.c. normal saline intravenously during the first hour of anesthesia; vomited bile within an hour; very dull; bad pulse; salivation; mere trace of phenolsulphonephthalein output.

Aug. 18: Found dead.

Necropsy Report.—Blood well clotted. *Thymus* remnant hemorrhagic. *Liver:* weight 332 gm.; extremely swollen and congested, with many hemorrhages; mucosa of *duodenum* very hemorrhagic; blood in lumen of gut farther down; autodigestion throughout. *Kidneys:* slightly full and hyperemic.

Microscopic Report.—Liver: about four fifths hemorrhagic necrosis, with heavy pigmentation, and trace of fat to lobule peripheries. *Lungs:* hemorrhage. Kidney: cloudy swelling and destruction of parenchyma. *Spleen:* congestion and pigmentation.

Drummond and Paton,[7] and others, have reported a diminished liver glycogen in acute epinephrin poisoning. No doubt the well known hyperglycemia and glycosuria has lent support to this work. Kuriyama[8] has recently published work on "The Adrenals in Relation to Carbohydrate Metabolism" in which he shows by liver analyses that starved rabbits given epinephrin have more liver glycogen than the controls. Subcutaneous injections caused an increase, sometimes of a thousand per cent. over the controls, in spite of the glycosuria. Even one dose of 1 mg. per kilo body weight given ten hours before sacrifice caused a marked increase over the control animal. Whipple and Christman[9] have shown that adrenal insufficiency causes a fall in phenoltetrachlorphthalein output in the bile.

Dog 19-10 in Experiment 47 shows a marked protection from two injections of epinephrin chlorid (see Control Experiment 51). The protection is still more noticeable in Experiment 48 from four injections. One dog was lost because too large a dose of epinephrin was given intravenously during chloroform anesthesia. Experiment 49 shows the effect of giving epinephrin shortly before the chloroform. In this case little, if any protection is demonstrable.

While these experiments were undertaken on the strength of Kuriyama's work, with the hope of showing a greater protection than in controls because of a difference in liver glycogen, we do not feel that any definite proof is furnished even though the results are clear cut. If all our feeding experiments pointed in the same direction, this would be corroboratory evidence for the influence of glycogen. Whatever the protective action of epinephrin may be, it seems to require time to develop, and is not an immediate effect of the drug.

Quinin sulphate is a drug supposed to decrease body metabolism;[10] probably in connection with this power, it favors the preservation of liver glycogen. Lepine and Porteret[11] found that guinea-pigs given quinin had 20 per cent. more liver glycogen than the controls. Nebelthau[12] corroborated these observations.

---

7. Drummond, W. B., and Paton, D. N.: J. Physiol. **21**:92, 1904.
8. Kuriyama, S.: J. Biol. Chem. **24**:269, 1918.
9. Whipple, G. H., and Christman, P. W.: J. Exper. M. **20**:297, 1914.
10. Sollmann, T.: A Manual of Pharmacology, W. B. Saunders Co., 1917, p. 455.
11. Lepine and Porteret: Compt. rend. de l'acad. de sc. **106**:1023, 1888. Cited by Salant, W.: Studies from the Rockefeller Institute for Medical Research **8**: 1908.
12. Nebelthau: Ztschr. f. Biol. **28**:138, 1891. Cited by Salant, W.: Studies from the Rockefeller Institute for Medical Research **8**: 1908.

Experiment 50 shows the protection afforded by quinin sulphate. Dog 18-124 had previously sustained an injury of ½ necrosis resulting from chloroform following starvation alone (see Experiment 23); the contrast in injury is very striking. Here again the evidence is in harmony with a glycogen protective theory.

Strychnin sulphate is a substance one of whose pharmacologic actions is supposed to be the reduction of liver glycogen. Experiment 53 shows the effect of giving relatively large doses on the two days

TABLE 9.—Potassium Cyanid, or Hydrazin Sulphate in Addition to Chloroform Anesthesia

Experiment	Starvation, Days	Supplementary Treatment	Chloroform, Hours	Liver Injury		Remarks
				Central Necrosis	Fat	
55 (Dog 19-54)	4	Potassium cyanid intravenously; ether anesthesia (control)	0	0	Heavy throughout	Died from distemper pneumonia on second day
56 (Dog 19-57)	0	Potassium cyanid intravenously; ether anesthesia	0	0	Moderate throughout	Distemper dog; toxic after injection; operation on third day
	4	Starvation only (control)	1¼	3/5	Slight, diffuse throughout	Operation on second day; dog died about 2 weeks later from combined effects of chloroform injury, operation and distemper
57 (Dog 19-81) Pup	0	Potassium cyanid intravenously during chloroform anesthesia	1	?	0	Brain diet for 4 days; previously showed no injury from chloroform alone after brain diet (see Exper. 12). Prostrated; died less than 5 hours after chloroform; central cells show granular degeneration
58 (Dog 19-80) Pup	3	Potassium cyanid intravenously during chloroform anesthesia	1	1/4	Trace	Not able to push the anesthesia on account of bad pulse and respiration; operation on second day
59 (Dog 19-87)	0	Potassium cyanid intravenously during chloroform anesthesia	1¼	1/2	Heavy in necrosis	Distemper dog; poor appetite (see Exper. 54). Cells surrounding necrosis are vacuolated; sacrificed on second day; low fibrin
60 (Dog 19-53)	4	375 mg. hydrazin sulphate subcutaneously (control)	0	0	Very intense throughout	Toxic; dead on second day; weighed 10.8 lbs. at time of injection
61 (Dog 19-59)	3	400 mg. hydrazin sulphate subcutaneously (control)	0	0	1/2; moderate	Quite sick; dead on second day; complicated by distemper and developing pneumonia; weight 17.5 lbs. at time of injection
62 (Dog 19-12)	4	240 mg. hydrazin sulphate subcutaneously on day preceding chloroform	1	Trace	Very intense throughout	Young, immature dog; toxic; distemper developed following chloroform; sacrifice; weight 16.5 lbs. at time of injection (see control, Ex. 51)

preceding chloroform anesthesia. The resulting injury is maximal under the conditions of starvation and chloroform, as is that in the case of Control Experiment 51. Dog 19-13, however, was somewhat older than Dog 19-11, and if maturity is a recognizable protection, perhaps the dog receiving strychnin may be considered to have received a slightly greater injury.

Experiments 53 and 54 were performed with a mixture of "toxic proteose" from three experimentally obstructed dogs. Such material is known to increase bodily catabolism, and from clinical observations probably interferes with oxidative processes. Dog 19-18 was given a dose which later work showed might have been fatal in itself, and in addition was given an hour and a quarter chloroform anesthesia. The result was great prostration, and death in less than twenty-four hours. The necropsy picture was that of proteose intoxication, but further, the liver showed four-fifths necrosis, which one certainly would not expect from the chloroform alone, after only three days' starvation. Dog 19-87 had not been starved, although eating poorly on account of distemper, and received a sublethal dose of proteose; the chloroform apparently caused very little injury.

EXPERIMENT 55.—*Cyanid Intravenously; No Chloroform (Control).*—Dog 19-54, a black and brown female mongrel.

Oct. 18: Wt., 17.38 lbs. Isolated for *starvation;* distemper severe; appetite poor.

Oct. 19 to 20: Starvation.

Oct. 21: Wt., 16 lbs.; 15 mg. KCN in 200 c.c. 0.9 per cent. NaCl intravenously during about one-half hour of ether anesthesia; preliminary increase in respiration followed by apnea, then shallow, slow breathing; apparently unconscious without ether; bounding pulse became flabby by end of injection; recovered from effects in about one hour; full diet.

Oct. 23: Found dead.

Necropsy Report.—Fibrino-purulent pleurisy, bronchopneumonia and pericarditis; liver looks orange-yellow—probably fatty.

Microscopic Report.—Liver: fat heavy throughout; engorged with blood; practically no necrosis. *Lungs:* extreme grade of pneumonia; no fibrin. *Kidneys:* cloudy swelling.

EXPERIMENT 56.—*Cyanid Intravenously; No Chloroform (Control).*—Dog 19-57, an old male collie.

Oct. 25: Wt., 63 lbs. Distemper dog; gave 53 mg. KCN in 300 c.c. saline intravenously.

Oct. 26 to 27: Eats some, but appears sick.

Oct. 28: *Piece of liver removed* at 1:45. Sections show no necrosis, but a moderate sprinkling of finely divided fat throughout.

EXPERIMENT 56.—*Chloroform Only.*—Dog 19-57, an old male collie.

Nov. 10: Wt., 60.9 lbs. Isolated for starvation; distemper practically disappeared; abdominal wound healed.

Nov. 11 to 12: No food.

Nov. 13: Wt., 57.6 lbs. Distemper flaring up again. *Chloroform for one and a quarter hours* (from 10 to 11:15 a. m.).

Nov. 15: Piece of liver removed at 1:30; considerable hemorrhage; sections show three fifths necrosis; fat slight, diffuse throughout. Dog died in about two weeks from combined effects of chloroform injury, operation and distemper.

EXPERIMENT 58.—*Potassium Cyanid Intravenously During Chloroform.*—Dog 19-89, a spotted female pup.

Dec 16: Isolated before daily feeding; starvation.

Dec. 17: Wt., 8.38 lbs. Bright and active; no food.

Dec. 18: Wt., 7.96 lbs. Bright and active; no food. *Chloroform for one hour* (from 10:20 to 11:20 a. m.). Gave 4 mg. KCN in 100 c.c. saline intravenously during three-quarters hour of anesthesia; could not push the anesthetic on account of bad pulse and respiration.

Dec. 17: Mixed diet.

Dec. 20: Wt., 8 lbs. *Piece of liver removed* at 1:30. Sections show a moderate injury; about one fourth necrosis, not at all uniform; a mere trace of fat.

Jan. 3: Died from distemper pneumonia.

EXPERIMENT 59.—*Potassium Cyanid Intravenously During Chloroform.*—Dog 19-87, a black and white female terrier.

Dec. 30: Wt., 12 lbs. Isolated; distemper very bad; abdominal wound (from previous operation) superficially open; eats very little. *Chloroform for one and a quarter hours* in a. m. Gave 8 mg. KCN in 160 c.c. physiologic sodium chlorid solution at intervals during anesthesia; was able to use chloroform quite freely.

Dec. 31: Dull; poor appetite.

Jan. 1, 1919: *Sacrificed* in a. m.; fibrin less than 100 mg. per 100 c.c. plasma.

Necropsy Report.—Viscera all pale from exsanguination; mediastinal lymph nodes hyperemic. *Liver* is orange-colored; lobule centers are prominent—probable necrosis. *Spleen* is small and fibrous. *Kidneys* are very flabby.

Microscopic Report.—Liver: approximately one half necrosis; fat in quite heavy deposits throughout the necrosis; cells in immediately surrounding zone are vacuolated considerably. *Kidneys:* slight cloudy swelling; abscess in medulla.

EXPERIMENT 61—*Hydrazin Sulphate Only (Control).*—Dog 19-59, a mongrel male bull.

Oct. 26: Isolated for starvation; distemper rather bad; mean tempered.

Oct. 27: No food.

Oct. 28: Wt., 17.5 lbs. Gave 400 mg hydrazin sulphate subcutaneously.

Oct. 29: Wt., 16.13 lbs. Quite sick.

Oct. 30: Found dead.

Necropsy Report.—Severe bronchitis and some pneumonia in left *lung;* blood clots all right. *Liver* and *spleen* quite engorged; probably a certain amount of diffuse fat in liver, but it does not show up very well. *Kidneys:* pale, suggesting fat.

Microscopic Report.—Lung: some pneumonia. *Spleen:* engorgement; pigment. *Liver:* central engorgement; pigment, especially in Kupfer cells; moderate amount of fat in central one half of lobules. *Kidneys:* cloudy swelling.

EXPERIMENT 62.—*Hydrazin Sulphate Previous to Chloroform.*—Dog 19-12, a black, half-grown male mongrel.

Aug. 5: Wt., 17.5 lbs. Isolated before daily feeding; *starvation;* in good condition; active.

Aug. 6: No food.

Aug. 7: Wt., 16.5 lbs. No food; 240 mg. hydrazin sulphate subcutaneously.

Aug. 8: Wt., 15 lbs. Quite dull. *Chloroform for one hour* (from 12:50 to 1:50).

Aug. 9: Wt., 15.2 lbs. Sick and droopy.

Aug. 10: Wt., 15.25 lbs. Beginning distemper; *sacrificed* in a. m.; blood urea, 20 mg.; urea N, 9 mg.

Necropsy Report.—Liver is extremely fatty; necrosis is not striking, although lobule centers generally show a dot orange to red in color; there is one spot of subcapsular hemorrhage 0.5 by 1 cm. near the hilum; other organs negative.

Microscopic Report.—Liver: about four fifths severely injured; small patches of frank necrosis; heavy deposits of fat to lobule peripheries.

In an article published in 1912, Graham[13] makes the statement that chloroform is one of a group whose effect on organs is like that of asphyxiation. He has later amplified this statement with the suggestion that many common anesthetic substances, including chloroform and ether, also carbon monoxid and potassium cyanid, are capable of dissociating in a manner which yields bivalent or unsaturated carbon. It is easy to imagine that such compounds might then appropriate oxygen within the body, in order to satisfy their free bonds.

Wells[14] has suggested that chloroform may unite with the cell lipoids, perhaps physically, then poison the protoplasm, probably by interfering with oxidatve and synthetic functions. Autolysis is not hindered, and the lipase continues its activity without the resulting products being oxidized; hence the fatty liver. Lactic acid is increased, which may possibly be correlated with the observation of Macleod and Wedd[15] that lactic acid is much increased in the hepatic blood if the liver oxygen supply is cut down, for instance, by temporarily clamping the hepatic artery and portal vein. Disintegration products accumulate and become toxic, aided by the impaired function of liver and kidneys. Whipple[16] has shown by the phenoltetrachlorphthalein liver test that in severe chloroform poisoning, the liver function goes down almost to zero.

Whipple[17] found that in moderate or severe chloroform injury the blood lipase is considerably above normal. Quinan[18] found that the liver lipase (or esterase) in such injuries may be decreased as much as 38 per cent. Jobling, Eggstein and Peterson[19] confirmed the observations of both Whipple and Quinan, but maintain that the increase in serum lipase is not liberated by the disintegrating liver cells, since the blood of the hepatic veins has a poorer content than the blood

13. Graham, E. A.: J. Exper. M. **15**:307, 1912; J. A. M. A. **69**:1666, 1917.
14. Wells, H. G.: J. A. M. A. **46**:341, 1906; Arch. Int. Med. **1**:589, 1908; Chemical Pathology, W. B. Saunders Co., 1918, Ed. 3.
15. Macleod, J. J. R., and Wedd, A. M.: J. Biol. Chem. **18**:447, 1914.
16. Whipple, G. H., and Speed, J. S.: J. Exper. M. **21**:203, 1915.
17. Whipple, G. H.: Bull. Johns Hopkins Hosp. **24**:1, 1913.
18. Quinan, C.: J. M. Res. **32**:73, 1915.
19. Jobling, J. W., Eggstein, A. A., and Peterson, W.: J. Exper. M. **22**:707, 1915.

elsewhere. Very recently Simonds[20] claims to have shown that neither the esterase nor the ereptase of the liver is appreciably affected by chloroform poisoning. Opie, Barker and Dochez[21] have shown that after chloroform or phosphorus poisoning, there is an increase in anti-enzyme (in the blood) for those enzymes active in alkaline mediums, perhaps compensatory to the liberation of the latter from the breaking down liver cells, and that the proteolytic enzyme of the blood stream which acts in an acid medium is increased in such conditions, perhaps, also, liberated from the liver; this last enzyme is held in check by the alkalinity of the blood.

Burge[22] has found that narcotics decrease the oxidative enzyme, catalase, in the blood stream, and believes that narcosis is due to decreased oxidation, following destruction of catalase in the nervous system. Consequent to the administration of chloroform, catalase drops 42 per cent. in fifteen minutes, while ether reduces catalase about 9 per cent. in the same length of time. At the end of one and one-half hours, however, the percentage reduction is more nearly the same, that from chloroform being 65 per cent., and that from ether 54 per cent. Burge's theory is that catalase is formed to a large extent in the liver, but some in the intestines, spleen, pancreas, etc. He thinks that oxidation controls autolysis, perhaps by oxidizing the autolytic enzymes under normal conditions. Ingestion of food increases the catalase of the blood and tissues parallel with the increase in heat production; the increase is due to stimulation of the liver by digestion products. Burge's work on narcotics supports the position of Verworn.[23]

Loeb and Wasteneys[24] have found a maximum reduction in oxidation of 20 per cent. in testing a number of narcotics, chloroform among the group; this they showed to be insufficient to produce asphyxiation.

Loevenhart[25] and his co-workers have done some very interesting work with cyanids and organic peroxids, such as iodoso- and iodoxybenzoic acids and their sodium salts. They find that, injected intravenously, cyanid intensifies, and the peroxids diminish inflammatory

20. Simonds, J. P.: J. Exper. M. **28**:663, 673, 1918.

21. Opie, E. L., Barker, B. I., and Dochez, A. R.: J. Exper. M. **13**:162, 1911.

22. Burge, W. E.: Am. J. Physiol. **43**:545, 1917; Science **46**:618, 1917; J. Pharm. and Exper. Therap. **12**: (Nov.) 1918. Burge, W. E., and Neill, A. J.: Am. J. Physiol. **43**:58, 1917; Ibid. **46**:117, 1918; Ibid. **47**:13, 1918. Burge, W. E., Neill, A. J., and Ashman, R.: Am. J. Physiol. **45**:388, 500, 1918.

23. Verworn, Max: Harvey Lectures **7**: 1911-1912.

24. Loeb, J., and Wasteneys, H.: J. Biol. Chem. **14**:517, 1913.

25. Loevenhart, A. S., and Grove, W. E.: J. Pharm. and Exper. Therap. **1**:289, 1909-1910; Ibid. **3**:101, 131, 1911-1912. Amberg, S., and Knox, J. H. M.: J. Pharm. and Exper. Therap. **3**:223, 1911-1912. Amberg, S., Loevenhart, A. S., and McClure, W. B.: J. Pharm. and Exper. Therap. **10**: (Sept.) 1917.

processes, such as the mustard oil reaction, and the intracutaneous reaction in serum sensitization. These results seem to be due to the effect on bodily oxidations and reductions. Furthermore, these workers[26] were able to produce central necrosis in rabbits' livers by suboxidation, the animals being left in an atmosphere of low oxygen tension for several days at a time.

It occurred to us that if chloroform causes liver injury primarily because it reduces oxidation, a substance such as potassium cyanid, whose action in that direction is well known, might intensify the effect of chloroform administration.

Experiment 55 indicates the result of injecting intravenously 1 mg. per pound body weight of potassium cyanid during ether anesthesia. The dosage caused quite severe prostration, but the liver two days later showed only fatty changes. Experiment 56 shows the comparative liver injury from 0.83 mg. potassium cyanid per pound body weight, and from one and one-fourth hours chloroform anesthesia following starvation. Here again the cyanid caused only fatty alterations, while chloroform gave the usual picture of severe necrosis.

Dog 19-81 (Experiment 57) had previously shown no liver necrosis from one hour's chloroform anesthesia following brain diet. In Experiment 57 this same dog received brain diet again, but at time of anesthesia received 1 mg. per pound body weight of potassium cyanid in addition to the chloroform. The pup never regained consciousness, and died about five hours later. The central cells (⅔) in the liver lobules look somewhat granular, and stained lighter than the peripheries; this picture was also seen after the chloroform alone, following brain diet. Manifestly, five hours is rather too soon after injury for chloroform necrosis to show clearly. Some of this liver tissue autolyzed in saline at body heat for six and one-half hours, also some left at room temperature over night, showed a greater tendency toward autolysis in the centers of the liver lobules. This experiment is unsatisfactory in many respects, but the action of potassium cyanid on the liver is not very marked.

In Experiment 58 the pup received only 0.5 mg. per pound body weight in addition to the chloroform anesthesia. The resulting necrosis is below the average for a pup starved three days and given one hour of chloroform anesthesia. Probably the pup did not receive quite as much chloroform as would have been the case had the cyanid not affected the pulse and respiration. The effect of the cyanid is not manifest.

---

26. Martin, G. H., Bunting, C. H., and Loevenhart, A. S.: J. Pharm. and Exper. Therap., Proc. **8**:112, 1916.

Dog 19-87 (Experiment 59) received ⅔ mg. cyanid per pound body weight in addition to one and one-fourth hours of chloroform anesthesia. Little trouble was had in administering the anesthetic in this case. The injury is greater than is to be expected in a fed animal from giving such an amount of chloroform; however, this dog had been suffering from severe distemper for some time, and under such conditions very little food is ever consumed; hence this dog was in an undernourished state approximating starvation, and a marked necrosis was to be expected. That the potassium cyanid influenced the amount of necrosis may be doubted.

Wells[27] has reported on the pathology of *hydrazin poisoning;* one of the most important findings is a more or less severe fatty degeneration of the liver. Underhill[28] and his co-workers have published a long series of papers dealing with the physiologic disturbances caused by hydrazin. Among other things, there is a marked hypoglycemia, and the glycogen content of the liver and muscles is reduced practically to zero. No specific influence is noticed on heat production, but the respiratory quotient shows an increased carbohydrate metabolism. Apparently the glyoxalase activity of the liver is not greatly altered by hydrazin. The blood fats are considerably increased, the maximum rise being coincident with the hypoglycemia.

In Experiments 60 and 61 hydrazin sulphate was given subcutaneously, and the liver injury was determined on the second day. Both dogs died; in Experiment 60, at least, death was undoubtedly due to hydrazin. In Experiment 62 a relatively small dose of hydrazin was given and one hour of chloroform anesthesia as is usually administered to pups. The fatty picture is comparable to that in Experiment 60, in which over twice as much hydrazin sulphate was given per pound body weight. It is noticeable that Dog 19-59 (Experiment 61) was nearly the same weight as Dog 19-12 (Experiment 62) and received much more hydrazin per pound, yet showed very much less fat. It may be concluded that the fatty picture in Experiment 62 could not have been caused by either the hydrazin or the chloroform alone. The small amount of frank necrosis is very striking. This phenomenon is hard to explain; Control Experiment 51 shows severe necrosis following starvation and chloroform anesthesia; if lack of liver glycogen predisposes to chloroform injury, Dog 19-12 should certainly reveal a marked necrosis, while as a matter of fact there is very little present.

---

27. Wells, H. G.: J. Exper. M. **10**:457, 1908.

28. Underhill, F. P., and Kleiner, I. S.: J. Biol. Chem **4**:165, 1908. Underhill, F. P.: J. Biol. Chem. **10**:159, 271, 1911-1912; **17**:293, 1914. Underhill, F. P., and Hogan, A. J.: J. Biol. Chem. **20**:203, 211, 1915. Underhill, F. P., and Martin, J. R.: J. Biol. Chem. **22**:499, 1915.

GENERAL DISCUSSION

The experiments reported in this paper naturally fall into three groups. The first group contains the experiments designed to repeat Graham's work on the protective action of carbonate solution against chloroform injury. Under carefully controlled conditions we cannot corroborate Graham's findings.

The second set of experiments was undertaken with the hope of sparing or diminishing the liver glycogen by means of drugs, to see whether such reactions affected the subsequent chloroform liver injury. Here the evidence is more or less contradictory; the epinephrin and quinin treatments fulfilled the requirements for which they were chosen, in so far as injury was lessened; whether this effect was a result of increased liver glycogen was not determined. Strychnin, supposed to lessen the liver glycogen content, did not cause any marked increase in chloroform injury. Hydrazin sulphate, also known to lessen liver glycogen content, caused an increase in fatty degeneration, but actually appeared to lessen necrosis. The status of liver glycogen in relation to chloroform liver injury is not settled as a result of these experiments.

The third group of experiments was designed to obtain evidence concerning the relation of bodily oxidations to chloroform liver necrosis. It would appear that large doses of "toxic proteose" intensify the injury, while small doses have no effect. Potassium cyanid has a very prostrating immediate effect, but seems to have very little influence on delayed liver injury and necrosis. The results of these experiments are hard to reconcile with a theory of chloroform necrosis due to lowered oxidation.

Although chloroform is losing favor as an anesthetic, it is still employed extensively by some physicians. In view of the frequent therapeutic use of such drugs as epinephrin and quinin it may be well to call attention to a possible practical value of these drugs. In cases of pernicious vomiting, for example, it would be very dangerous to use chloroform because of the starved tissues, but it might be possible to lessen the probable liver injury by means of the drugs mentioned.

SUMMARY

Sodium carbonate in hypertonic salt solution given intravenously during chloroform anesthesia has no protective action against the resultant liver injury.

Phosphate solutions, high in buffer content, have no protective action against chloroform liver injury.

Epinephrin subcutaneously or intramuscularly in the days preceding chloroform anesthesia exerts a distinct protective action against

chloroform liver injury. The resistance requires time to develop, and is not demonstrable by a single dose of epinephrin a short time before chloroform administration.

Quinin sulphate given in the days preceding chloroform exerts a marked protective action against liver injury.

Hydrazin sulphate, although itself injurious to the liver, apparently does not intensify (perhaps lessens) the toxic action of chloroform.

It would appear that strychnin sulphate has very little deleterious action on an ordinary chloroform injury following starvation.

Toxic proteose solutions in large dosage may intensify the chloroform injury, but in small amount seems to have no effect.

Potassium cyanid given intravenously during chloroform anesthesia, although very toxic at the time, seems to exert little, if any, influence on the delayed chloroform poisoning (liver injury).

The hypothesis that glycogen protects the liver cell against the injury of chloroform will not explain all the observed facts. Some of our experiments are in harmony with this hypothesis, but others are equally positive against it. This simple explanation of the resistance of liver cells to chloroform injury does not suffice, and undoubtedly other factors are concerned which must be searched out.

The hypothesis that chloroform injury and liver necrosis is to be explained by a lowering of the level of tissue oxidation (tissue asphyxia) receives no support from our experiments.

The peculiar protective action of epinephrin and quinin sulphate in chloroform poisoning may have some practical clinical application.

BOOK REVIEW

RADIO-DIAGNOSIS OF PLEURO-PULMONARY AFFECTIONS. By F. Barjon. Translated by James A. Honeij, M.D., Assistant Professor of Medicine in Charge of Radiography, Yale Medical School. Cloth. Price, $2.50. Pp. 183, with illustrations. New Haven: Yale University Press, 1918.

The roentgen-ray examination of the lungs has become an indispensable clinical method. It is astonishing how rapidly it has forced a way to an acknowledged position beside more time-honored methods. But on account of this rapid advance it has been difficult to keep pace with its progress. Some have greeted it with the indifference and suspicion always accorded a parvenu; others have acclaimed it with the exaggerated enthusiasm always bestowed on a new and brilliant arrival. Between the indifferent and the partisan, it has usually been either too coolly or too warmly received. Only a few sober minds have paused to weigh critically its pretensions and to guide it to the place justly deserved. There is great need at present that some one properly endowed should present these pretensions in a warm but unbiased way, so that the method may be saved from the extravagance of its overzealous friends and still receive proper recognition. Here is a work from a skilled technician and a physician of wide experience and rare judgment. Barjon's book is an attempt to meet this need. It is the most meritorious contribution to the subject that has yet appeared, although it falls far short of the desired treatise. It is too sketchy, too brief, too provincial. A few French authors are cited, but otherwise the whole mass of valuable material contributed by numerous investigators is completely ignored. In spite of these shortcomings, however, the book may be recommended as a concise and satisfactory guide to the subject.

Unfortunately, the author is introduced to his American audience in an unattractive garb. The translation is no doubt faithful, but the French idiom is preserved, and the language is not only unattractive but in some places difficult to interpret.